EXHIBIT A

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(54) **CRUSH-RESISTANT OXYCODONE TABLETS INTENDED FOR PREVENTING ACCIDENTAL MISUSE AND UNLAWFUL DIVERSION**

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(57) **ABSTRACT**

Water-insoluble matrix tablets based on oxycodone or one of its pharmaceutically acceptable salts and capable of prolonged release of oxycodone to the body, exhibiting a crush resistance of at least 4 MPa.

Figure 1

Dissolution profiles at pH 6.8 of non-film coated 40 mg oxycodone HCl tablets, obtained according to Example 1.

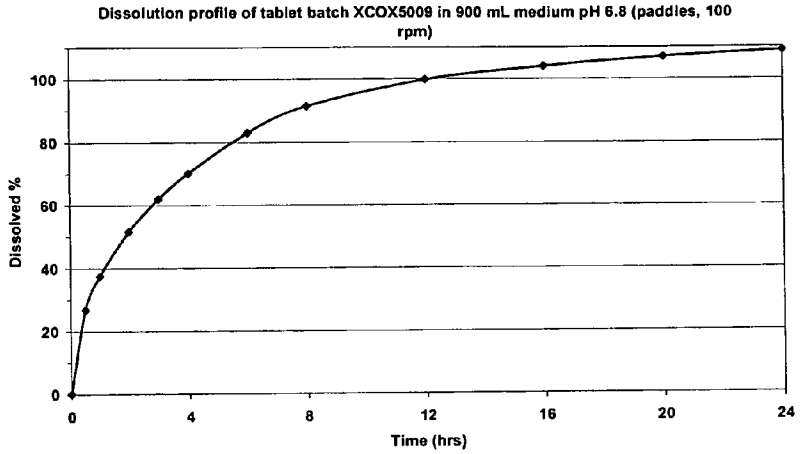


Figure 2

Dissolution profiles at pH 6.8 of non-film coated 40 mg oxycodone HCl tablets, obtained according to Example 2.

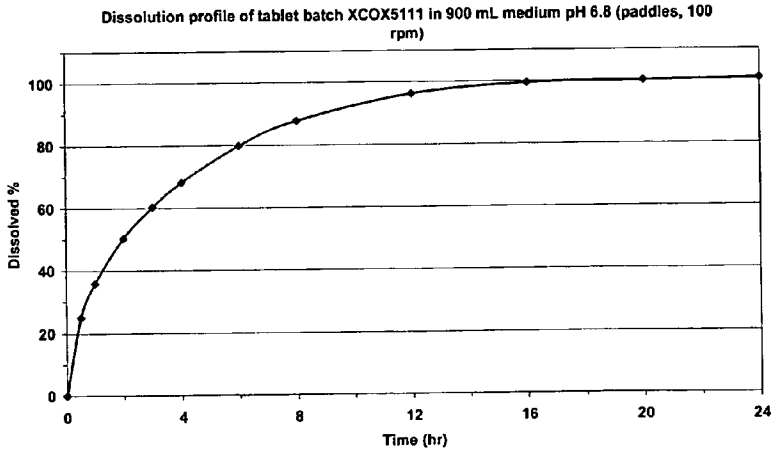


Figure 3

Dissolution profile at pH 6.8 of tablets conforming to Example 2, film-coated with a layer of Ethylcellulose EC30 D and subjected to a curing step

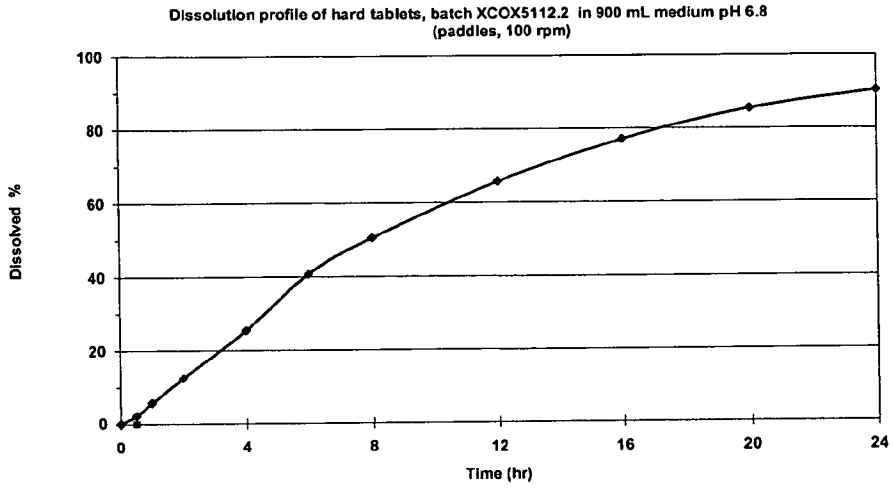


Figure 4

Comparative dissolution profiles of oxycodone matrix tablets conforming to the invention in an ethanol-free 0.1 N HCl medium and in a 0.1 N HCl medium containing 40 % ethanol

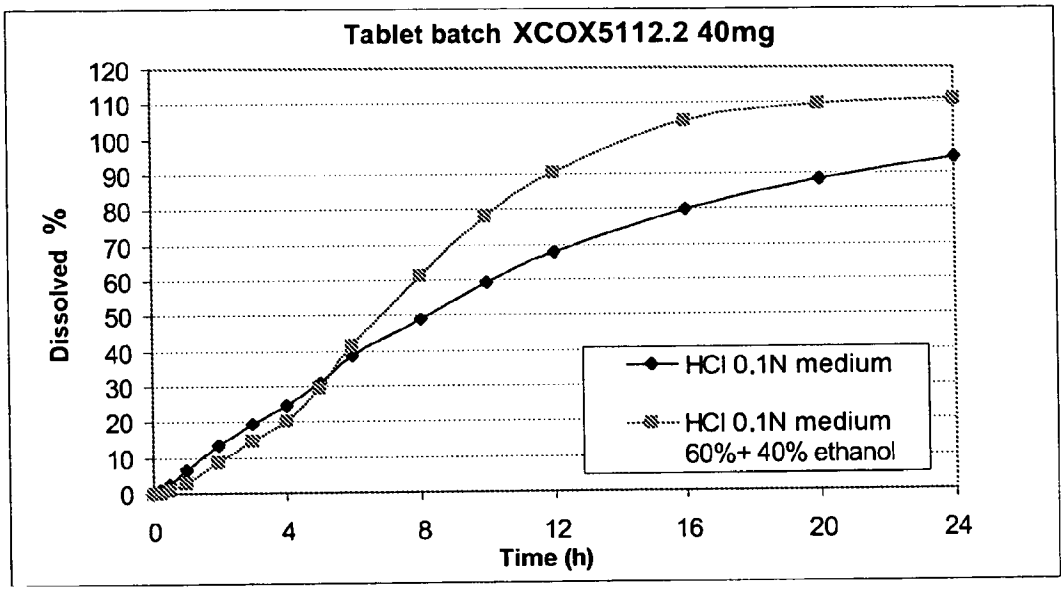


Figure 5

Dissolution profiles of oxycodone matrix tablets conforming to the invention in two dissolution media of different pH (1.2 and 6.8)

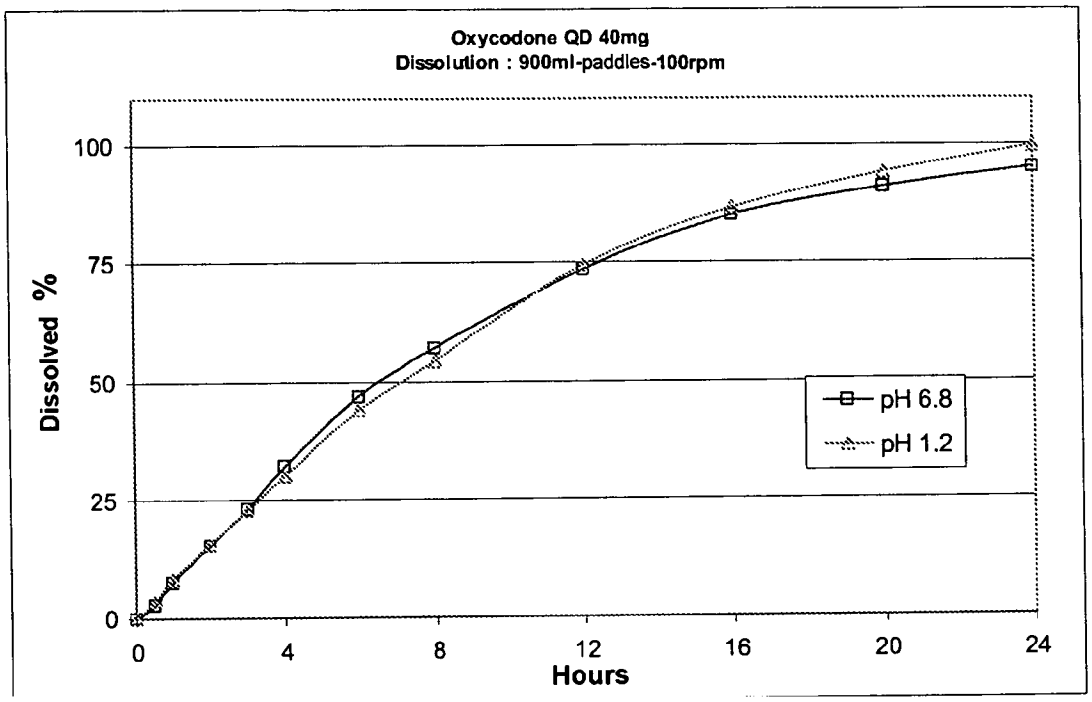


Figure 6

24-hour dissolution profiles of 40 mg oxycodone tablets conforming to the invention after a storage period in Al/Al blister pack under accelerated stability conditions of 1 month, 2 months, 3 months and 6 months.

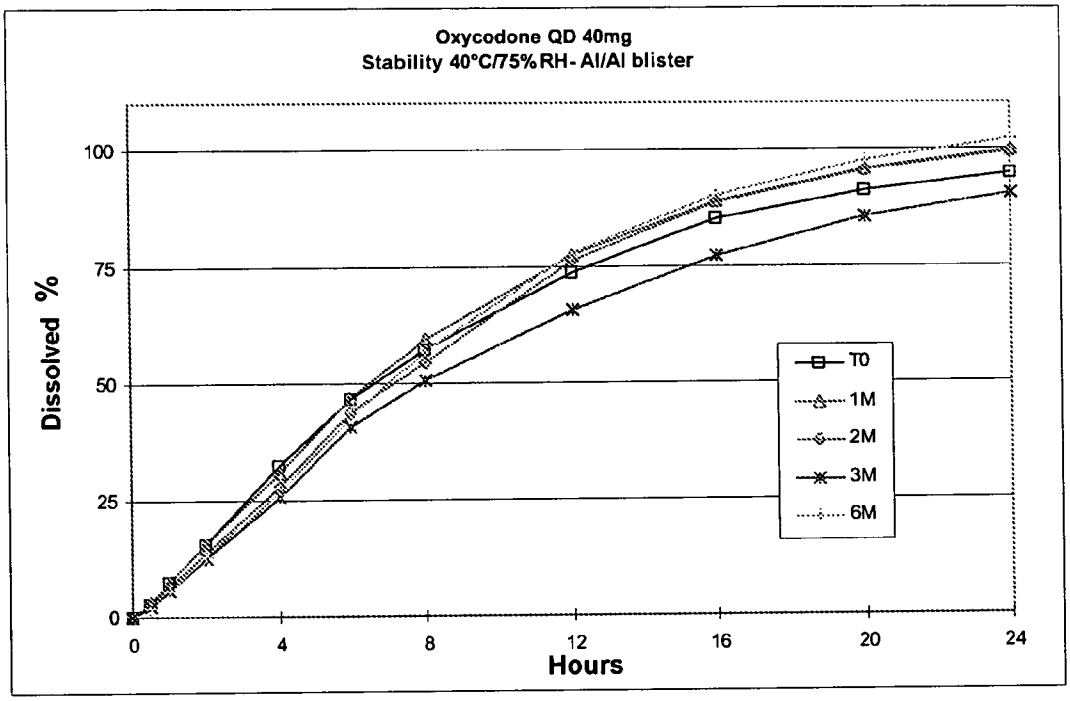


Figure 7

24-hour dissolution profiles of 20 mg oxycodone tablets conforming to the invention after a storage period in HDPE bottles with desiccant under accelerated stability conditions of 1 month, 2 months and 3 months.

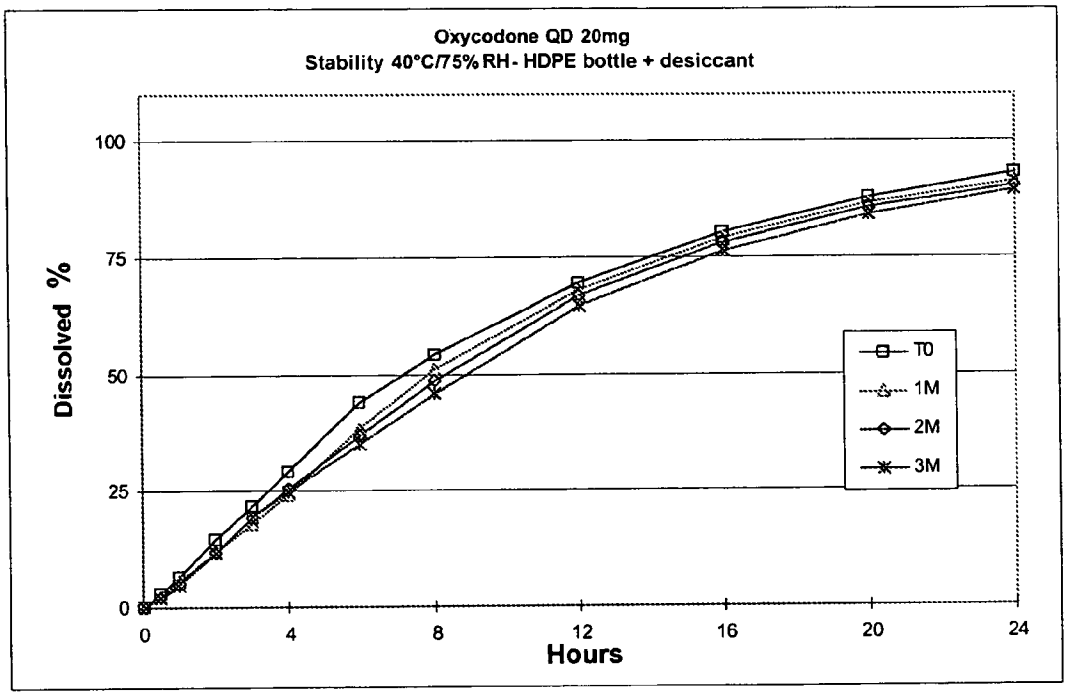


Figure 8

Plasma profiles of oxycodone after once-a-day administering of 40 mg oxycodone tablets conforming to the invention, and 40 mg oxycodone tablets of the reference product Oxycontin®

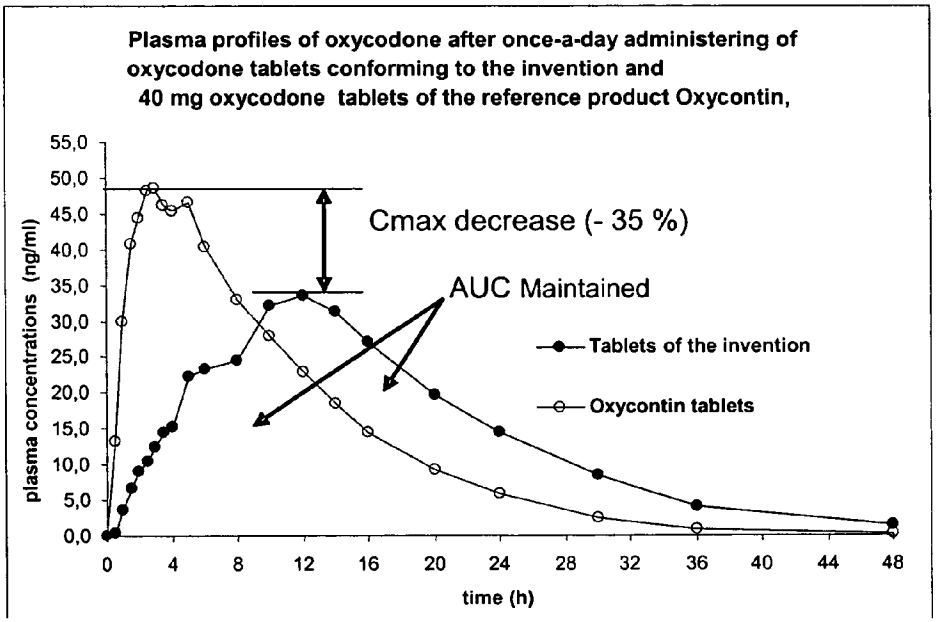


Figure 9

24-hour dissolution profile of ultra-hard non-coated tablets containing oxycodone and naloxone, at pH 6.8.

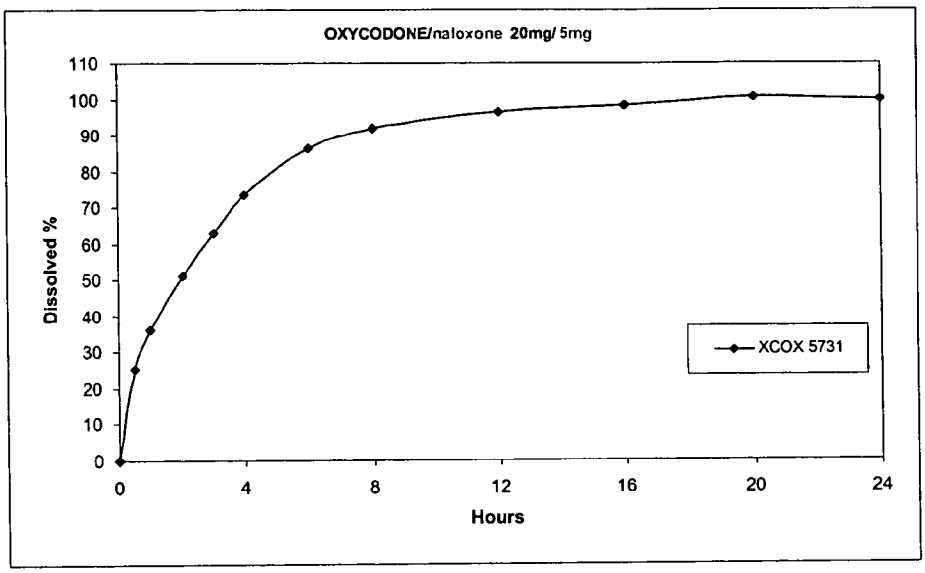


Figure 10

10-hour dissolution profiles at pH 6.8 of ultra-hard, non-coated 20 mg oxycodone tablets comprising a matrix containing mineral excipients

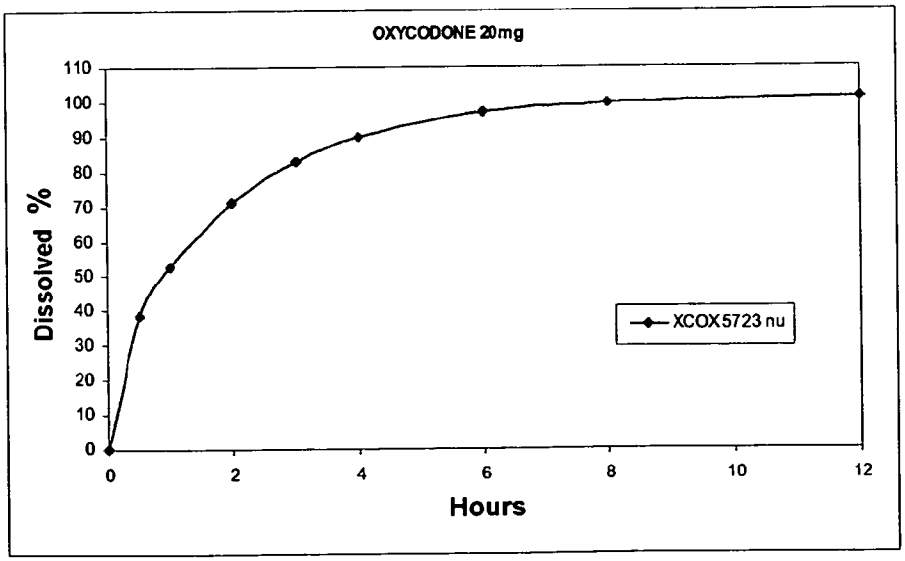
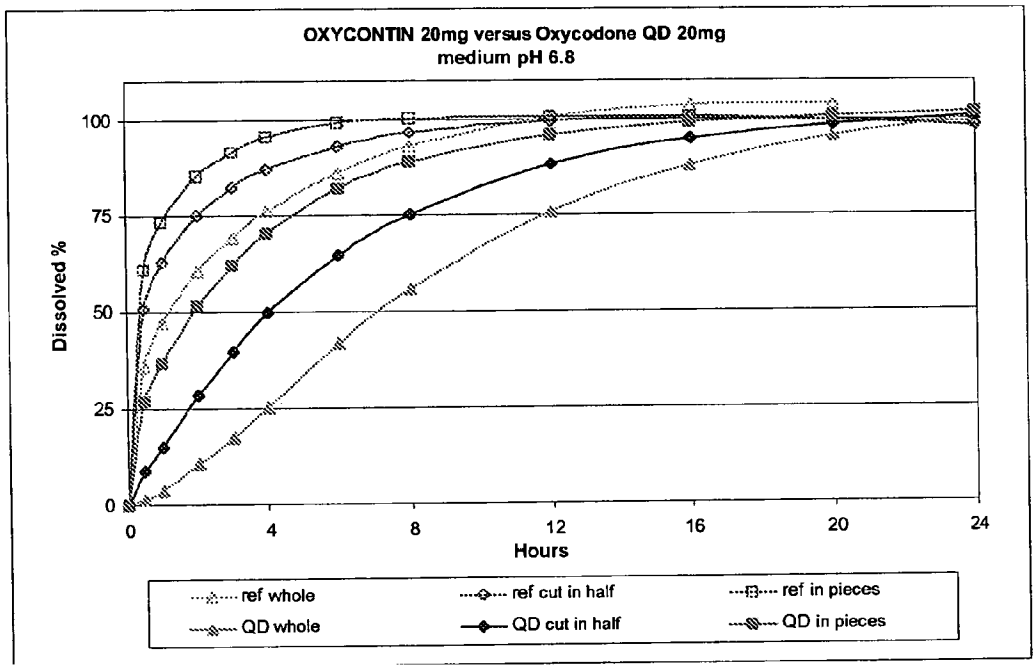


Figure 11

Dissolution profiles of tablets conforming to the invention(« QD ») and tablets of the reference product Oxycontin® (ref) at pH 6.8, for whole tablets, tablets cut in half, or crushed (« in pieces »)



CRUSH-RESISTANT OXYCODONE TABLETS INTENDED FOR PREVENTING ACCIDENTAL MISUSE AND UNLAWFUL DIVERSION

[0001] The present invention concerns insoluble matrix tablets having very high crush resistance.

[0002] These matrix tablets which are unbreakable under usual conditions, non-friable and insoluble in an aqueous medium, are of particular interest as reservoirs for psychotropic agents since they can reduce and even prevent addictive abuse of these substances by crushing, dissolving and injection, or by crushing and inhalation.

[0003] The present invention also concerns the method to obtain said tablets and their use for sustained-release oral administering of the active ingredients, and in particular of psychotropic active ingredients.

[0004] With respect to tablets containing sustained-release opiate agents, in particular oxycodone, the phenomenon of accidental misuse may assume several aspects. First, it may arise from failure to heed administering conditions. It may happen that the tablet, intended to be swallowed, is accidentally chewed by the patient. The consequences of full or partial destruction of the tablet whose structure is intended to delay the release of the active ingredient, can prove to be dangerous and even fatal for the patient (excess dosage leading overdose). This is the reason why the leaflet supplied with the drug OxyContin® LP specifically states that «The tablets must be swallowed whole without being chewed» .

[0005] Also, accidental misuse of drugs containing sustained-release oxycodone has also been observed when patients simultaneously, or within a short time interval, ingest the drug with a strong dose of alcohol.

[0006] It has effectively been observed with a sustained-release form of hydromorphone that the presence of alcohol in the stomach deteriorated the layer of excipients designed for sustained release of the active ingredient, leading to release into the body of a major quantity of active ingredient («dose-dumping»), once again the cause of a dangerous overdose.

[0007] The leaflet supplied with OxyContin® LP for example indicates in the list of contraindications that the consumption of alcohol is to be avoided with this drug.

[0008] Similarly, in the United States, the FDA (Food and Drug Administration) gives a serious warning to patients treated with OxyContin® not to consume alcoholic drinks during the period of treatment (see in particular: http://www.fda.gov/cder/drug/infopage/oxycontin/oxycont in-qa.htm).

[0009] There is therefore a real need to prevent this type of accidental misuse to increase patient safety, whilst maintaining a simple, comfortable route of administration (oral route).

[0010] Since the placing on the French pharmaceutical market in 1990 of substitute treatments for opiate drugs, in the form of sublingual tablets (Temgésic®) initially packed in a form for injection, an increase has been observed in the phenomenon of abuse of certain psychotropic agents by drug addicts.

[0011] The term deliberate misuse or illicit use (or more usually "drug-abuse") is used to qualify the use of certain medicinal products for addiction purposes, in particular the use of certain psychotropic or narcotic agents e.g. opioids or their derivatives intended to treat severe pain or to treat addiction to opiate drugs.

[0012] Abuse by parenteral/nasal route of sustained-release active ingredients normally intended for oral route, gives drug addicts the opportunity to achieve immediate, accumulated psychotropic effects of the total active ingredient dose present in the initial formulation.

[0013] For example, in the particular case of buprenorphine, a powerful opioid analgesic initially sold as a preparation under the name Temgesic® for the substitution treatment of drug addiction, it is estimated that 25% to 30% of the treatments sold are given abuse by parenteral or nasal route. The same applies to the preparation called Subutex® (sublingual tablets with high buprenorphine dosage manufactured by Schering-Plough) officially used as substitution treatment in tens of thousands of opioid drug addicts, for which it is estimated that 34% of consumers abuse the drug by injection and approximately 30% by nasal route.

[0014] Yet the phenomenon of drug abuse is also seen with preparations intended to treat severe pain, such as morphine sulphate (Skenan®) and oxycodone for example (Moscontin®, OxyContin® LP) or moderate pain (Neocodion®). These sustained-release forms contain large quantities of opioids intended to limit pain over long periods, and abuse thereof gives rise to the massive release of morphine derivatives.

[0015] Drug abuse also affects other classes of therapeutic drugs, in particular benzodiazepines (Rohypnol®), and to a lesser extent certain neurological treatments (Artane® Antiparkinson drug).

[0016] As a result, these therapeutic or substitution treatments, in some cases accessible by mere prescription, and whose dosage can reach up to ten or so tablets a day, are subject to two chief modes of abuse: parenteral administration (injection) and nasal administration (inhalation).

[0017] With regard to abuse by injection, the tablet or capsule containing the active ingredients of interest is reduced to a fine powder using any possible means available to the drug addict, in particular a mortar or lighter, even simply by chewing or biting the tablet. The rough powder obtained, which necessarily contains the excipients initially present in the pharmaceutical form, can then be dissolved in a small volume of liquid (a few millilitres) sometimes previously heated and/or to which an acid is added for certain active ingredients present in base form (brown heroin, base morphine). The liquid obtained can then be roughly filtered to limit the entry of large particles into the bloodstream, using a cigarette filter for example, before it is injected via intravenous route.

[0018] In this case, the active ingredient then becomes immediately available in the bloodstream, since there is no longer any excipient to delay its release, giving rise to an immediate psychotropic effect sought by drug addicts.

[0019] Abuse by inhalation also consists of crushing the pharmaceutical form until a sufficiently fine powder is obtained to render the active ingredient accessible to the micro-vessels of the intranasal mucous membrane. Here again, the action of the sustained-release excipients, designed for oral administration, is fully ineffective and the expected immediate psychotropic effect is able to be achieved.

[0020] Drug abuse is also accompanied by numerous health risks related directly to injection or inhalation of the excipients and of non-purified crush residues, little or ill-filtered and non-sterile. Recent studies report that some tampered tablets are sometimes dissolved directly in the syringe, then injected without any prior filtering, this practice being directly responsible for numerous deaths through pulmonary embolism.

Additionally, the addition of acids in non-sterile liquid form (lemon juice) to the crush residues is apparently also responsible for the transmission of bacterial or mycosal pathologies (candidiasis).

[0021] These practices therefore come to increase the already high risks of viral and bacterial transmissions and complications of dermatological type (abscesses, necrosis) related to the parenteral injection itself. Also, regarding the injection of Subutex® tablets, the presence of corn starch in the tablet formulation is responsible for the onset of oedema due to this excipient which, once injected, accumulates in the lymph and venous systems leading to swelling of the lower limbs.

[0022] To limit these problems, one approach consists of associating the active ingredient in one same pharmaceutical form with an agent capable of limiting the psychotropic effect when the formulation is taken by parenteral route.

[0023] This is the case for example with formulations combining methadone and naloxone, initially described in patents U.S. Pat. No. 3,966,940 and U.S. Pat. No. 3,773,955.

[0024] This abuse-deterrent formulation was reproduced in the particular case of buprenorphine. Patent EP 0 185 472 for example describes an oral formulation of buprenorphine also containing an effective dose of naloxone, which acts as competing antagonist at the morphone receptors. Since naloxone has only very slight bio-availability via oral route, it little hinders the analgesic action of buprenorphine when the medicinal product is administered conventionally per os. On the other hand, when subject to abuse by parenteral route, naxolone becomes fully available and inhibits the analgesic action of buprenorphine. With this type of chemical association, however, the oral pharmaceutical form remains crushable and soluble in an aqueous medium.

[0025] One sublingual formulation combining naltrexone with buprenorphine has also been described in patent EP 0 319 243. With said association, it is possible in particular to increase the antagonist effect of naltrexone with respect to opioids, whilst providing consumers with a non-euphorigenic, analgesic sensation even if the composition is abused by parenteral route. This type of formulation therefore has little appeal for a drug addict and contributes towards curbing the phenomenon of drug abuse. However, this approach necessarily has recourse to the co-administering of two active ingredients, leading to increased production costs and sale price of the medicinal product.

[0026] Still using an approach combining the association of the opioid with an antagonist agent, patent application US 2003/0143269 describes a pharmaceutical form in which the opioid and the antagonist are interdispersed so that the antagonist is "sequestered" in a compartment preventing it from being released when the medicinal product is taken normally by oral route. On the other hand, if the product is tampered with by crushing, deterioration of the structure leads to mixing of the two active agents and to inhibition of the sought after psychotropic effect.

[0027] In this approach, the pharmaceutical form has a predominant role to play against abuse. However, here again the chemical association of two compounds is necessary, leading to a complex manufacturing process and high production costs.

[0028] Also, patent application US 2003/0068392 describes a pharmaceutical form in which the opioid agent is associated not only with an antagonist, but also with an irritant agent sequestered in a closed compartment. Tampering with the pharmaceutical form inevitably leads to release of the irritant. This form therefore requires the association of three active agents, and the creation of compartmented areas, which makes its manufacture complex and more costly than a simple pharmaceutical form such as a tablet.

[0029] Other companies have developed pharmaceutical systems in which the opioid or substance which may be subject to abuse is not associated with an antagonist. For example, patent application US 2005/0281748 teaches the manufacture of an oral dosage pharmaceutical form in which the opioid agent of interest is modified so as to increase its lipophilicity, by forming a salt between the active agent and one or more fatty acids.

[0030] This pharmaceutical form allows the sustained release of the active ingredient when it is taken by oral route, since the enzymes of the gastrointestinal tract gradually break down the groups of fatty acids, releasing the active ingredient as and when they are broken down.

[0031] On the other hand, any physical tampering of the pharmaceutical form releases microparticles of active ingredient coated with an insoluble layer, preventing the immediate release of the active ingredient in an aqueous medium. Said formulation requires chemical conversion of the active ingredient.

[0032] Patent application US 2003/0118641 describes an oral dosage form of opioid with sustained release, in which the active opioid ingredient is associated with a hydrophilic polymer matrix and a cationic resin. Since the resin carries opposite charges to the active ingredient, it binds to this ingredient within the polymer matrix, preventing its extraction.

[0033] Said pharmaceutical form renders the active compound inseparable from the excipients responsible for its sustained release in the body, even if usually available solvents are used (hot water, alcohol, vinegar, hydrogen peroxide, etc . . .).

[0034] Some companies have developed pharmaceutical systems containing gels. For example Pain Therapeutics Inc. and Durect use a biodegradable gel which can be administered via oral or parenteral route, consisting of an agent with high viscosity: Sucrose Acetate Iso Butyrate (SAIB). This gel allows sustained release of an opioid agent, oxycodone. This type of gel, which is the subject of patents U.S. Pat. No. 5,747,058 and U.S. Pat. No. 6,413,536 maintains its capacity to release the active ingredient controllably over periods of 12 to 24 hours, even if the capsules containing the same are deteriorated or crushed. The main interest of these pharmaceutical forms lies in the fact that the oxycodone cannot be extracted from its gel carrier, and cannot be injected either via parenteral route owing to the very high viscosity of these formulations (Remoxy® product using ORADUR® and SABER® technologies currently undergoing phase III clinical trials).

[0035] Said gels also have the capacity to resist extraction of oxycodone in the presence of an alcohol or acid, the active ingredient remaining trapped in the network formed by the gelling agent.

[0036] These gel-containing pharmaceutical forms are complex formulations, which firstly require the use of high viscosity liquids at industrial level, giving rise to restricted handling, and secondly entail major restrictions with regard to packaging (use of bottles of vials), which is not the case with tablets.

[0037] Means are also known with which to manufacture matrix tablets of very high hardness. Patent EP 0 974 355 describes tablets obtained by granulating a hydrosoluble vitamin mixed with at least one additive of saccharide type, in the presence of a conventional polymer binder such as HPMC for example. Said tablets, intended for swift release of the hydrosoluble vitamin in the body, have high hardness strength, in the order of 20 to 30 kp/cm^2 (kiloponds/cm^2), which is equivalent to hardness values of approximately 1.96 to 2.94 MPa. Although relatively hard and consisting of more than 90% hydrosoluble vitamin and of excipients that are also hydrosoluble (HPMC, saccharides), these tablets disintegrate rapidly in the body (disintegration time in the region of 10 to 15 minutes). Said tablets are firstly fully unsuitable for sustained release of the active ingredient, and secondly are easily dissolved in an aqueous medium, making them unfit for use as pharmaceutical form for substances which may be given abuse.

[0038] Patent EP 0 933 079 describes matrix tablets having a crush resistance varying from around 1 MPa (1 N/mm^2) up to 10 MPa. Said tablets are obtained from a treated starch powder that can be directly compressed. However, these tablets are intended for the rapid release of active ingredients, since they have a relatively short disintegration time in an aqueous medium, in the order of approximately 6 to 7 minutes. Owing to their rapid disintegration in an aqueous medium these tablets, here again, cannot be used to convey active ingredients which are liable to be given abuse and which are intended to be released over long time periods.

[0039] Patent EP 0 997 143 describes the production of bi-convex matrix tablets of very high hardness (up to 1.1 MPa i.e. around 11 kp/cm^2) and with a friability of less than 1%, obtained after compressing a matrix consisting chiefly of a compressible, disintegratable carbohydrate (generally mannitol) and a binder. Said chewable tablets, even if they have very high hardness in the solid state, dissolve in an aqueous medium and after a very short period of time in the mouth, and therefore rapidly release the active ingredient into the body.

[0040] The manufacture of matrix tablets intended for the sustained release of an active substance in the body, and also having high hardness, is taught by patent U.S. Pat. No. 6,592,901. In this document, tablets are obtained having good compressibility characteristics and containing a particular grade of ethylcellulose (non-ionic ethyl ether of cellulose—sold under the trade name Aqualon®), that is pH-independent, highly substituted and of low viscosity. The crush resistance of the tablets thus obtained is in the order of 10 to 20 kp (kiloponds) which, scaled down to the size of tablets, is equivalent to around 1.4-2.8 MPa. Also, this special grade of ethylcellulose is water-insoluble, limiting the diffusion of liquids and hence release of the active ingredient in the body. Release of the active ingredient is achieved slowly since the tablets obtained from this model show a release profile in which less than 80% of the active ingredient is released after 24 hours.

[0041] Matrix tablets having very strong crush resistance are also described in the work by Pontier et al. (Pontier et al. *Journal of European Ceramic Society*, 22 (2002)). In particular, the authors show that it is possible to obtain very hard matrix tablets using mineral excipients of the calcium phosphate family, such as tricalcium phosphate or hydroxyapatite, by direct compression. For example, from a tricalcium phosphate powder, previously granulated then compressed under compression forces in the order of 300 MPa, it is possible to obtain tablets whose crush resistance (tensile strength) can reach 6.5 MPa. However, this article does not give any information on the capacity of such tablets to release one or more active ingredients over an extended period of time, nor the capacity of such pharmaceutical structures to remain intact in an aqueous medium.

[0042] Thesis research on apatitic calcium phosphate compression by C. Pontier ("*Les phosphates de calcium apatitiques en compression. De la chimie aux qualités d'usage*" *Thèse de l'Université de Paris XI*, presented on 25 Sep. 2001) shows that it is possible, after compression, to obtain matrix tablets containing calcium phosphates (hydroxyapatite and tricalcium phosphate in particular), having very high crush resistance possibly reaching 7 MPa.

[0043] Said tablets also have the capability of releasing theophylline in an aqueous medium over a long period of time (60% of active ingredient released in 8 hours) by gradual diffusion through the matrix pores. However, this article does not allow any conclusion to be drawn on the capacities of said tablets to remain intact in an aqueous medium, and hence to resist abuse by crushing in a liquid medium.

[0044] Patent application US 2005/0031546 concerns an abuse-deterrent pharmaceutical form containing one or more active ingredients liable to give rise to addiction, and at least one synthetic or natural polymer necessarily having a tensile strength of at least 500 N. The only polymer specifically described is ethylene polyoxide having a molecular weight of 7 000 000 optionally associated with an xanthane gum. These tablets can be prepared using a method which comprises a compression step preceded by a heat exposure step, concomitant with a heat exposure step or followed by a heat exposure step. Therefore the heat exposure step is necessary to obtain the desired hardness. This step, even if of short duration, is firstly not applicable to heat-sensitive active ingredients and secondly requires the use of special equipment and extra energy consumption which contributes towards increasing the cost of the process.

[0045] There is therefore a true need for the development of a pharmaceutical form which allows the safe administering of active ingredients having a psychotropic effect and which are released over an extended period of time i.e. which has a pharmaceutical structure which makes both its crushing and its dissolution highly difficult or even impossible, and further which prevents the extraction and separation of the active ingredient from the agents responsible for its sustained release. In addition, it must be possible for this pharmaceutical form to be produced using an extremely simple manufacturing method, that is rapid and low cost.

[0046] The applicant has unexpectedly found a novel, solid, oral pharmaceutical formulation prepared simply in the form of sustained-release matrix tablets, that are both insoluble and ultra-hard. With said tablets, it is possible to prevent the phenomenon of accidental misuse and to curb and even eliminate the phenomenon of drug abuse.

[0047] The subject-matter of the invention is therefore water-insoluble matrix tablets, capable of releasing one or more active ingredients into the body over extended periods, preferably over periods of more than 12 hours and further preferably more than 20 hours, containing oxycodone dispersed in a compression matrix, said matrix consisting of at least one excipient chosen from the group comprising sustained-release, water-insoluble, pH-independent polymers, mineral excipients and their mixtures, the quantity of said excipient and the compression conditions being chosen so

that said tablets have a crush resistance of at least 4 MPa, advantageously at least 6 MPa.

[0048] Advantageously, the compression conditions do not necessarily entail a heating step of the mixture to be compressed, or of the compression tooling either before or during the actual compression step.

[0049] Preferably the tablets conforming to the invention are used to produce pharmaceutical forms capable of releasing the oxycodone they contain over a period of 24 hours, making it possible to administer the oxycodone in a once-a-day formulation.

[0050] Under the present invention, the terms deliberate misuse or drug abuse are used to designate any intentional deterioration of pharmaceutical forms. In particular, the notion of drug abuse concerns reducing the tablets to powder, then inhaling this powder or dissolving it in a small quantity of liquid for its parenteral injection.

[0051] The term matrix tablet is used to designate a tablet whose inner structure is homogeneous and identical from the core towards the periphery of the tablet. Therefore the tablets of the present invention consist of a homogeneous mixture of oxycodone in powder or granule form and of a compression matrix containing at least one excipient chosen from the group comprising sustained-release, water-insoluble, pH-independent polymers, mineral excipients and their mixtures.

[0052] Under the present invention, the term compression matrix is used to designate all the excipients which take part in the cohesion of the tablet. Said compression matrix is both water-insoluble and has a certain permeability (hydrophilic matrix) or a porous network (inert matrix) responsible for gradual release of the active ingredient, which does not vary in relation to the pH conditions of the medium.

[0053] The term «compression mixture» in the present application is used to designate all the constituents of the tablet (oxycodone, whether granulated or not, and the constituents of the compression matrix) before their compression into tablet form.

[0054] In the present application, the notions of crush resistance and of hardness are both used to characterize the tablets. Hardness characterizes the tensile strength of the tablet under a diametral-compression test. A round tablet is placed between two jaws, one of which is fixed and the other mobile. Hardness corresponds to the force applied by the mobile jaw which causes rupture of the tablet into two more or less equal parts. It is expressed in Newtons (N) or Kilonewtons (kN) (see European Pharmacopoeia: ref: 01/2005:20908).

[0055] Crush resistance is inferred from measurement of hardness: it is a parameter which takes into account the surface area of the tablet exposed to the force, and corresponds to strength per unit surface area expressed in Pascals (Pa) or Megapascals (MPa), 1 MPa corresponding to 1 Newton per mm^2. Crush resistance is a parameter of particular interest to compare the behaviour of tablets with different surface areas, since it does not require recourse to the parameter of tablet size. Its calculation formula is the following (as per «Determination of tablet strength by the diametral-compression test» .Fell, J. T.; Newton, J. M. J. Pharm. Sci., 59 (5): 688-691 (1970)):

$$Rd = \frac{2 \times F}{\pi \times D \times h}$$

in which:

[0056] Rd is the diametral tablet breaking load (in MPa)

[0057] F is the hardness of the tablet (in N)

[0058] D is the diameter of the tablet (in mm)

[0059] H is the thickness of the tablet (in mm).

[0060] In the present application, the expression «sustained-release» polymers is used to designate polymers routinely used in the pharmaceutical industry to control the release of an active ingredient into its dissolution medium. In the present application, the sustained-release polymers used are water-insoluble, which means that release of the active ingredient into the surrounding medium occurs exclusively via a phenomenon of simple diffusion, with no erosion or gradual disintegration of the polymer. These polymers effectively have certain permeability vis-à-vis the surrounding medium, responsible for gradual diffusion of the active ingredient out of the polymer matrix. Therefore the lower the permeability of the polymer, the more the diffusion of the active ingredient is sustained.

[0061] Under the present invention, the expression pH-independent polymers is used to designate those polymers capable of forming a permeable network or matrix, and whose permeability is not influenced by the pH of the surrounding medium.

[0062] Under the present invention, the expression pharmaceutically acceptable salts of oxycodone is used to designate salts which are pharmaceutically equivalent to the base, in particular oxycodone sulphate, oxycodone hydrochloride, oxycodone trifluoroacetate, oxycodone thiosemicarbazone hydrochloride, oxycodone pentafluoropropionate, p-nitrophenylhydrazone oxycodone, o-methyloxine oxycodone, thiosemicarbazone oxycodone, semicarbazone oxycodone, phenylhydrazone oxycodone, hydrazone oxycodone, oxycodone hydrobromide, oxycodone mucate, oxycodone methylbromide, oxycodone oleate, n-oxide oxycodone, oxycodone acetate, dibasic oxycodone phosphate, oxycodone, monobasic oxycodone phosphate, inorganic or organic salts of oxycodone, oxycodone acetatetrihydrate, oxycodone bis (heptafluorobutyrate), oxycodone bis(methylcarbamate), oxycodone bis (pentafluoropropionate), oxycodone bis (pyridine-3-carboxylate), oxycodone bis (trifluoroacetate), oxycodone bitartrate, oxycodone chlorohydrate and oxycodone pentahydrate sulfate.

[0063] The tablets of the invention are tablets with very high hardness (hereunder called «ultra-hard tablets»). Their structure is such that their crushing cannot be envisaged using conventional domestic techniques, and their dissolution in an aqueous medium, even an acidified medium, is practically impossible.

[0064] This extreme hardness is also accompanied by little or no friability, which means that these tablets are a pharmaceutical form of choice for oxycodone which can be given drug abuse. This very low or non-friability makes the tablets practically unbreakable using conventional or domestic techniques (spoon, mortar, lighter . . .).

[0065] The tablets of the invention are also practically insoluble in an aqueous medium, even at low pH (pH<3). These characteristics make them difficult to administer via parenteral route.

[0066] The tablets of the invention are also insoluble in an alcohol medium, which means that they can be taken even if alcohol is ingested, thereby avoiding accidental misuse.

[0067] Additionally, the tablets of the invention, despite their extremely hard, resistant outer structure, allow sustained release of the oxycodone contained in said matrix. The tablets

of the invention therefore allow release of oxycodone into the body over a period that is greater than 8 hours, preferably greater than 12 hours, further preferably greater than 20 hours.

[0068] Advantageously, the tablets of the invention are used to produce pharmaceutical forms containing oxycodone to be taken once-a-day.

[0069] Finally the matrix structure of the tablet according to the invention, consisting of a mixture of known sustained-release excipients approved for oral use and of granules containing the active ingredient, is extremely simple, allowing for its easy industrial production since it requires a simple compression step of the mixture without the need to heat the compression tooling and/or mixture to be compressed either before or during the actual compression step.

[0070] Advantageously, the compression matrix of the tablets conforming to the invention represents 50 to 98 weight % of the total weight of the tablets, further advantageously 85 and 95 weight % of the total weight of the said tablets.

[0071] The excipients, which can be used alone or in a mixture in the matrix composition of the tablets of the invention, can be of organic type; they then belong to the group comprising cellulose derivatives and in particular microcrystalline cellulose (e.g. that sold under the trade name Avicel®) and ethylcellulose (e.g. that sold under the trade name Aqualon®), the polymers of the family of water-insoluble, pH-independent methacrylic acids, in particular the grades Eudragit® RL 12.5, RL PO & RL 100 and RS 12.5, RS PO and RS 100, the derivatives of polyvinylalcohols, the polymers of lactic and glycolic acids (PLGA), starches, waxes, derivatives of polyvinyl acetates, derivatives of polyvinylpyrrolidone and mixtures of polymers such as the mixture of microcrystalline cellulose and [polyvinyl acetate/polyvinylpyrrolidone (80:20)] (sold under the trade name Kollidon SR®) and the mixture of microcrystalline cellulose and [poly (ethylacrylate/methylmethacrylate/trimethylamonioethyl methacrylate chloride) (1:2:0.2)].

[0072] Advantageously, the sustained-release, water-insoluble, pH-independent polymers of the present invention belong to the group comprising cellulose derivatives, the mixture of microcrystalline cellulose and [polyvinyl acetate/polyvinylpyrrolidone (80:20)] (sold under the trade name Kollidon SR®) and the mixture of microcrystalline cellulose and [poly(ethylacrylate/methylmethacrylate/trimethylamonioethyl methacrylate chloride) (1:2:0.2)].

[0073] The excipients of the compression matrix can also be of mineral type: they then belong to the group comprising calcium phosphates (in particular dicalcium or tricalcium phosphates), aluminium and silicon silicates, and magnesium carbonates.

[0074] The compression matrix of the tablets according to the invention can advantageously consist of a mixture of several of the above-mentioned excipients. It may be a mixture of organic polymers such as microcrystalline cellulose and of vinyl derivatives in variable proportions, or a mixture of organic polymer+mineral derivative such as a mixture of calcium and silicon silicate+microcrystalline cellulose in variable proportions.

[0075] The excipients present in the compression matrix of the tablets conforming to the present invention advantageously represent between 40 and 100 weight % of the total weight of said matrix, advantageously 50 to 90 weight % of the total weight of the matrix.

[0076] According to one advantageous embodiment of the invention, the compression matrix consists of a (1:1) mixture of two polymers, advantageously it consists of a (1:1) mixture of microcrystalline cellulose and of the mixture [polyvinyl acetate/polyvinylpyrrolidone to a proportion of 80:20 (sold under the trade name Kollidon SR®)], or a mixture of microcrystalline cellulose and [polyethylacrylate/methylmethacrylate/trimethyl-amonioethyl methacrylate chloride in proportions of (1:2:0.2)]. Advantageously, these two polymers each represent a weight proportion in the order of 40% of the total weight of said compression matrix.

[0077] The compression matrix can advantageously, in addition to the excipients of the compression matrix, contain one or more excipients intended to promote the conducting of the compression process such as anti-adherent agents e.g. colloidal silica, talc, magnesium stearate, Polyethylene Glycol (PEG) or calcium stearate, or to promote cohesion of the tablets on compressing such as binders conventionally used for this purpose, in particular starches, cellulose derivatives, or fillers, lubricants, plasticizers, bulking agents, or sweeteners or colouring agents.

[0078] If present, these excipients are used conventionally to the proportion of 0.1 to 10 weight % of the total weight of the compression matrix, preferably between 0.5 and 5 weight %.

[0079] Said compression matrix may also comprise at least one the following substances (a) to (f) or a mixture thereof:

[0080] (a) a substance which irritates the nasal and/or pharyngeal tracts,

[0081] (b) an agent increasing viscosity, allowing the formation of a gel when the tablet is dissolved in a minimum amount of water,

[0082] (c) an antagonist of oxycodone,

[0083] (d) an emetic substance,

[0084] (e) a colouring agent as aversive agent,

[0085] (f) a bittering substance.

[0086] The antagonist (c) is advantageously chosen from the group comprising naloxone, naltrexone, nalmefene, nalid, nalmexone, nalorphine and naluphine, these different compounds each being either in a pharmaceutically acceptable form, in particular a base or salt, or a solvated form. These antagonists are present in doses conventionally used, in particular to the proportion of 0.1 to 100 mg per tablet.

[0087] In one advantageous embodiment of the invention, said antagonist agent is naloxone or one of its pharmaceutically acceptable salts.

[0088] The tablets conforming to the invention are therefore of particular interest as reservoirs for oxycodone, an active ingredient which may be the subject of drug abuse and intended to be released into the body over periods of more than 8 hours, preferably more than 12 hours, and further preferably more than 20 hours.

[0089] The oxycodone contained in the tablets of the invention can be present in any form known to those skilled in the art, in particular in powder, crystal or granule form.

[0090] Preferably, the tablets of the invention are used to produce once-a-day pharmaceutical dosage forms.

[0091] The oxycodone contained in the tablets of the invention can represent between 5 and 70 weight % of the total weight of the tablet. Advantageously the oxycodone represent 10 to 50 weight % of the total weight of the tablet. It can be added directly to the mixture to be compressed, coated on carriers (to obtain microgranules) or wet- or dry-granulated (to obtain granules).

[0092] If the oxycodone is in the form of microgranules, these microgranules can be obtained conventionally by depositing (coating) the active ingredient(s) on the surface of pharmaceutically neutral carriers, such as pre-manufactured microspheres containing cellulose or a mixture of sugar and starch sold under the name "neutral cores" or "sugar spheres", or they may be granules of other excipients such as lactose for example.

[0093] The depositing (coating) method of the active ingredient is a conventional method known to those skilled in the art. Therefore depositing (coating) can be made by spraying a solution or suspension of oxycodone onto the surface of the neutral carrier, or by spraying the oxycodone in powder form onto the surface of the carrier previously moistened with a binder solution.

[0094] The granules of oxycodone may also be obtained by dry or wet granulation of the active ingredients of interest, generally in the presence of at least one binding agent and optionally a wetting agent, depending on techniques, here again well known to those skilled in the art.

[0095] The granules thus obtained are mixed with the excipients of the compression matrix, and the mixture is then compressed.

[0096] The exceptional hardness of the tablets conforming to the invention can be obtained without it being necessary to apply a heating step, before or during compression, either to the mixture to be compressed (compression matrix and oxycodone) and/or to the compression tooling (press).

[0097] Advantageously, the granules have a diameter allowing a good compression yield, i.e. generally between 100 and 600 μm.

[0098] According to another embodiment of the invention, and if particle size so permits, the oxycodone is mixed directly with the excipients forming the compression matrix, then the mixture is directly compressed.

[0099] Finally, another possible embodiment of the invention consists of mixing the oxycodone with the excipient(s) of the compression matrix, then dry- or wet-granulating this mixture to obtain directly compressible granules.

[0100] The tablets conforming to the invention can be of any shape and size allowing tablets of high hardness to be obtained. Advantageously the total surface area of the tablet is less than 150 mm^2.

[0101] The present invention is therefore suitable for the production of tablets with either low or high doses of active ingredient.

[0102] According to one particular embodiment of the invention, the tablets can be film-coated with an outer coating which those skilled in the art will know how to adapt in relation to needs and the intended function of this coating.

[0103] For example, the outer coating can be applied for the purpose of protecting the active ingredient, if it is a labile active ingredient sensitive to the low pH values of the gastric medium for example, in which case the term gastroresistant coating is used.

[0104] Also, the outer coating can be applied to further delay diffusion of the active ingredient through the matrix. For this purpose different grades of ethylcellulose can be used, or of methacrylic polymers well known to the skilled person.

[0105] Finally, the outer coating can be used to modify the cosmetic appearance of the tablet (texture, colour) and/or palatability (taste/feel in the mouth) for the patient. In particular, excipients can advantageously be used such as cellulose derivatives or acrylic derivatives well known to those skilled in the art, to mask the taste of the active ingredient if necessary.

[0106] Said coating can therefore consist of a mixture of one or more excipients of different type known to those skilled in the art, used either alone or in a mixture for the different functions listed above.

[0107] The excipient(s) used for coating are applied in a manner known to those skilled in the art, in the necessary quantity to obtain the desired function(s).

[0108] These excipients can be applied to the surface of the tablet in conventional manner by spraying a solution or suspension of coating agent in a solvent, in a perforated pan or fluidised bed for example.

[0109] The present invention also concerns the method to manufacture the tablets of the invention. This method comprises the following steps:

- **[0110]** mixing the oxycodone with the excipient(s) of the compression matrix,
- **[0111]** optional granulation, and
- **[0112]** compressing said mixture under conditions chosen so that said tablet has a crush resistance of at least 4 MPa, advantageously at least 6 MPa,
- **[0113]** optional coating of the tablet.

[0114] If the coating polymer of the tablet is a sustained-release polymer, the coated tablets conforming to the invention can advantageously undergo a curing step of said coating polymer to guarantee its physical and chemical stability. This step is conducted under controlled temperature conditions, below the melt temperature of the active ingredient, and for a controlled time which is dependent upon the coating polymer and which may last between 1 minute and several months, with a relative humidity rate of 50 to 99%. This step can be conducted in an oven or pan.

[0115] The active ingredient can be mixed directly in the compression matrix, or mixed in the form of previously prepared granules or microgranules. This granulation step improves the uniform resistance of the tablets produced. Preferably, for granules, wet-granulation is used (aqueous or organic), or for microgranules the active ingredient is deposited by spray-coating in solution or suspension onto neutral carriers.

[0116] Compression is performed on a rotary compressing machine with pre-compression station. The compression parameters must be chosen so that the hardness of the tablets obtained is adapted to the present invention. However, it is not necessary to apply any heating step either before and/or during compression to the mixture to be compressed or to the compression tooling, for the purpose of achieving the exceptional hardness observed with the tablets of the invention. The applied compression forces lie between 10 kN and 160 kN, advantageously between 30 kN and 80 kN. They are chosen to be compatible with the punch material and so that they can be used at industrial production rates, whilst allowing tablets to be obtained whose tensile strength is greater than 4 MPa, and preferably greater than 6 MPa.

[0117] Examples 1 to 10 and FIGS. **1** to **14** given below are intended to illustrate the invention but do not in any way limit its scope.

[0118] FIG. **1** gives the dissolution profile in phosphate buffer medium pH 6.8 (monopotassium phosphate/disodium phosphate) of 40 mg oxycodone HCl tablets, non-film coated, obtained according to example 1.

[0119] FIG. **2** gives the dissolution profile at pH 6.8 of non-film coated, 40 mg oxycodone HCl tablets, obtained according to example 2.

[0120] FIG. **3** gives the dissolution profile at pH 6.8 of tablets conforming to example 2, film-coated with a layer of ethylcellulose EC30 D, which have undergone curing under the conditions of example 3.

[0121] FIG. **4** gives the comparative dissolution profiles of oxycodone matrix tablets according to the invention in an ethanol-free 0.1 N HCl medium, and in a 0.1 N HCl medium containing 40% ethanol such as measured according to example 4.

[0122] FIG. **5** illustrates the dissolution profiles of oxycodone matrix tablets conforming to the invention in two dissolution media of different pH (1.2 and 6.8) following the operating mode described in example 4.

[0123] FIG. **6** illustrates the 24-hour dissolution profiles of 40 mg oxycodone tablets conforming to the invention, after a storage period in alu/alu blister packs under accelerated stability conditions of 1 month, 2 months, 3 months and 6 months under the conditions of example 4.

[0124] FIG. **7** illustrates the 24-hour dissolution profiles of 20 mg oxycodone tablets conforming to the invention, after a storage period in HDPE bottles with a desiccant under conditions of accelerated stability of 1 month, 2 months and 3 months.

[0125] FIG. **8** gives the plasma profiles of oxycodone after once-a-day administering of 40 mg oxycodone tablets conforming to the invention, and 40 mg oxycodone tablets of the reference product OxyContin®, according to example 4.

[0126] FIG. **9** illustrates the 24-hour dissolution profile, at pH 6.8, of ultra-hard, non-coated tablets of oxycodone and naloxone, according to example 5.

[0127] FIG. **10** illustrates the 10-hour dissolution profiles, at pH 6.8, of non-coated, ultra-hard tablets containing 20 mg oxycodone.

[0128] FIG. **11** illustrates the dissolution profiles observed with tablets conforming to the invention («QD») and tablets of the reference product OxyContin® (ref) at pH 6, 8, for whole tablets, tablets cut in half or crushed tablets («in pieces»)

EXAMPLE 1

Manufacture of Tablets Containing Granules Obtained by Granulating Oxycodone HCl and 4.87% HPMC and Containing a Compression Matrix Consisting of a (1:1) Mixture of Two Excipients [Microcrystalline Cellulose and (PVA/Povidone 80:20)]

1. Preparation of the Tablets

1.1. Preparation of Oxycodone Granules

[0129] The granules are obtained by wet granulation of the active ingredient (oxycodone HCl, batch NO DV000165; McFarlan Smith, England) and hydroxypropylmethylcellulose (HPMC grade Pharmacoat® 606, Brenntag) acting as binder. Granulation is conducted in a fluidised bed (GCPG-1, Würster, Glatt, Germany) by bottom-spraying a solution of the binder (HPMC) onto the powdered active ingredient.

[0130] Oxycodone is added to the fluidised bed and placed in sustentation. The binder solution is sprayed onto the powder which aggregates to form granules. Water is progressively removed by evaporation and after a final drying step. The final drying step in an oven (16 hours at 60° C.) is conducted to obtain an acceptable final water content (less than 6%).

[0131] The proportions of HPMC and oxycodone are given in Table 1.

TABLE 1

	Batch n° of granules XOXY4979	
Ingredients	Percentage [%]	Wt. in grams/batch
Oxycodone HCl	95.13	500.0
HPMC (Pharmacoat ® 606)	4.87	25.6
Purified water	—	336.9
Total (dry)	100.0	525.6

[0132] The parameters for the granulation process are given in Table 2: phase 1 corresponds to spraying of the first 175 g of solution, phase 2 corresponds to spraying of the remaining 185 g:

TABLE 2

	Batch n° of granules XOXY4979	
Step	1	2
Input temperature (° C.)	40	45
Output temperature (° C.)	23-29	24-27
Product temperature (° C.)	21-28	25-27
Spray pressure (bar)	1.0	1.2
Spray rate (g/min)	10.0	6.0
Drying step (oven)	16 hours at 60° C.	

[0133] The granules obtained after the fluidised bed step have the characteristics indicated in Table 3.

TABLE 3

Batch number	Mean particle size (μm)	Apparent density g/mL	Flow time (Sec./100 g)	Relative humidity (%)
XOXY4979 (4.87% HPMC)	108.7	0.450	6	3.47

1.2. Preparation of the Compression Matrix

[0134] A pre-mixture of microcrystalline cellulose (Avicel™ PH102, FMC) and precipitated silica (Syloïd® 244, Keyser & Mc Kay) is formed in a cubic mixer (AR 401, Erweka) for 2 min at 40 rpm. The mixture of polyvinylacetate/povidone (80:20) (Kollidon® SR, BASF) and the oxycodone granules prepared as described under step 1.1 are added to the pre-mixture and homogenisation is conducted in the cubic mixer for 15 minutes at 40 rpm. Finally, the lubricant (magnesium stearate, Quimdis) intended to limit sticking and friction during compression is added to the preceding mixture using the mixing parameters: 5 minutes at 40 rpm.

[0135] The quantity of oxycodone granules used is determined with a view to producing tablets containing 40 mg oxycodone.

[0136] The proportions of each of the excipients are summarized in Table 4.

TABLE 4

Ingredients	Batch number XCOX5009 Percentage [%]	Weight (mg/tablet)
Oxycodone granules (lotXOXY4979)	19.83	44.62
Kollidon ® SR	39.74	89.40
Avicel ® PH102	39.73	89.40
Syloid ® 244	0.20	0.45
Magnesium stearate	0.50	1.13
Total	100.00	225.00

1.3. Compression

[0137] The compression step of the final mixture obtained in the preceding step is conducted on a compression press (PR-12, Sviac) with a compression force of 35 kN using oblong punches 11 mm×5 mm. Compression is conducted conventionally, without the mixture to be compressed or the compression tools being subjected to a heating step either before or during the actual compression step.

[0138] The characteristics of the tablets obtained are summarized in Table 5. The mean values correspond to the mean calculated for 20 tablets.

TABLE 5

Batch n° of tablets	XCOX5009
Weight (mg)	225
Shape	oblong
Size (mm)	11 × 5
Thickness (mm)	4.15
Hardness (N)	381
Crush resistance (MPa)	6
Friability (%)	0.0

The tablets obtained following Example 1 have very high crush resistance, 6 Mpa, and zero friability, without there being any need to heat the matrix constituents or the compression press before or during compression.

1.4. Dissolution Profile of the Tablets Obtained According to Example 1

[0139] The tablets obtained according to Example 1 have hardness and friability characteristics which make them practically unbreakable, meaning that they are excellent candidates for a pharmaceutical medium which can limit abuse thereof by crushing.

[0140] Additionally, the applicant has evidenced that these tablets are practically insoluble in an aqueous medium, even if acid: on completion of the dissolution tests (over 24 h) the tablets remain intact at the bottom of the dissolution vessel, both in a pH 6.8 buffered medium, and in a pH 1.2 acid medium.

2. Dissolution Method

[0141] Measurement of the dissolution of the tablets obtained in Example 1 is performed in 900 mL of phosphate buffer, pH 6.8 (monopotassium phosphate/disodium phosphate) using the rotating paddle method with a paddle rotating speed of 100 rpm (Type II paddle apparatus in accordance with the American Pharmacopoeia USP 24).

[0142] The dissolution medium is continuously analysed by chromatography (HPLC) with UV detection. For each sample, measurement is performed on at least three vessels.

[0143] The results of the dissolution tests are summarized in FIG. **1**.

[0144] Unexpectedly, it is observed that the tablets of the invention, even though they are insoluble, nevertheless have the capacity to release the active ingredient they contain over an extended period, i.e. over periods of more than 8 hours, preferably more than 12 hours, and further preferably more than 20 hours.

[0145] Said tablets are therefore of particular interest for the production of pharmaceutical forms of «Once-a-Day» type, i.e. only requiring one administering per day.

EXAMPLE 2

Manufacture of Tablets Containing Granules Obtained by Granulating Oxycodone and 6.46% HPMC and Containing a Compression Matrix Consisting of a (1:1) Mixture of Two Excipients (Microcrystalline Cellulose and PVA/Povidone 80:20)

[0146] In this example, the applicant sought to determine the influence of the quantity of binder used during the granulation step on the dissolution profile of the tablets.

[0147] The granulation step is identical to the step described to produce tablets conforming to Example 1, with the sole exception that this time the quantity of binder (HPMC, Pharmacoat® 606) is 6.46 weight % of the total weight of the granules. The composition of these granules is summarized in Table 6.

TABLE 6

Ingredients	Tablet batch n° XOXY5103 Percentage [%]	Weight (g/batch)
Oxycodone HCl	93.54	590.5
HPMC (Pharmacoat ® 606)	6.46	40.8
Purified water	—	483.9
Total (dry)	100.0	631.3

[0148] The mixing and compression steps are then conducted following exactly the same parameters as in Example 1, using the same qualitative and quantitative formula.

[0149] The characteristics of the tablets obtained according to Example 2 are summarized in Table 7. The mean values correspond to the mean calculated per 10 or 20 tablets.

TABLE 7

Batch n° of tablets	XCOX5111
Weight (mg)	227.0
Shape	Oblong
Size (mm)	11 × 5
Thickness (mm)	4.2
Hardness (Newtons)	397
Crush resistance (MPa)	6
Friability (%)	0.0

[0150] The tablets obtained following Example 2 show very strong crush resistance, equal to 6 Mpa, and zero friability. No heating step before or during compression was necessary to obtain tablets of such hardness.

[0151] The dissolution profile of these tablets is then determined as described in Example 1. This profile is illustrated FIG. **2**.

[0152] The quantity of binder used has little influence on the release kinetics which extend over 24 h.

EXAMPLE 3

Tablets Obtained According to Example 2, Film-Coated with an Outer Coating of Aquacoat® ECD-30 (Ethylcellulose)

[0153] In this example, an assessment is made of the influence of an outer coating applied to the oxycodone tablets obtained following Example 2. Here again, no heating step was applied either to the mixture to be compressed or to the compression tooling, whether before or during the actual compression.

1. Preparation of the Tablets

1.1. Sub-Coating

[0154] Prior to coating with the actual polymer, a sub-coating step is applied to the tablets obtained in Example 2.

[0155] This sub-coat is intended to improve the surface condition of the tablets. It consists of a mixture of HPMC (Pharmacoat® 603), an anti-foaming agent (Simethicone, Dow Corning), a lubricant (micronised talc, Luzenac (Univar) and anti-static agent (Syloid 244, Keyser & McKay), the HPMC representing a weight gain of 3% relative to the total weight of the uncoated tablets. The proportions of each of the excipients are given in Table 8.

TABLE 8

Ingredients	Batch n° of tablets XCOX5112.1 Percentage [%]	Weight/pan (g)	Weight (mg/tablet)
Tablets XCOX5111	95.96	1000.0	227.00
HPMC (603)	2.88	30.0	6.81
Simethicone (dry weight)	0.01	0.1	0.02
Talc	0.86	9.0	2.03
Syloid ® 244	0.29	3.0	0.69
Purifd. water**	N/A	308.5	N/A
Total (dry)	100.00	1042.07	234.5

**Note: the water is removed during the process;
N/A: Not Applicable

[0156] This sub-coating is performed in conventional manner in a perforated pan (Trislot).

[0157] The parameters for the coating process are summarized in Table 9.

TABLE 9

Batch n° of tablets	XOXY5112.1
Input temperature (° C.)	38
Output temperature (° C.)	32
Pan rotation speed(rpm)	15
Air flow rate (m^3/h)	150
Spray pressure (MPa)	0.12
Spray rate (g/min)	2.0-2.6

1.2. Coating

[0158] The actual coating of the previously sub-coated tablets is performed in a perforated pan (Trislot).

[0159] Coating is conducted using an aqueous dispersion of ethylcellulose (Aquacoat® ECD-30, FMC) the proportion of ethylcellulose representing 2.87 weight % of the total weight of the coated tablets. The proportion of the different excipients is given in Table 10. Here again, no specific heating step of the tablets was performed, either before or during application of the sub-coat or the actual coating.

TABLE 10

Ingredients	Batch n° of tablets XCOX5112.2 Percentage [%]	weight/pan (g)
Tablets of batch XCOX5112.1	95.75	1042.09
Aquacoat ® ECD-30 (sec)	2.87	31.24
Dibutyl sebacate	0.69	7.51
Talc	0.52	5.66
Syloïd ® 244	0.17	1.85
Purified water**	N/A	185.04
Total (dry)	100.00	1088.35

**Note:
the water is removed during the process; N/A: Not Applicable

[0160] The parameters of the coating process are reproduced in Table 11.

TABLE 11

Batch n° of tablets	XCOX5112.2
Input temperature (° C.)	40
Output temperature (° C.)	34
Pan rotation speed (rpm)	15
Air flow rate (m^3/h)	140
Spray pressure (MPa)	0.12
Spray rate (g/min)	1.5-2.0
Curing step	XCOX4976.2
Input temperature (° C.)	75
Output temperature (° C.)	65
Product temperature (° C.)	60
Pan rotation speed (rpm)	3
Air flow rate (m^3/h)	140
Time (hours)	24

1.3. Curing Step

[0161] This is conducted in a perforated pan after coating, for 24 hours at 60° C. to allow stabilization of the film coating.

[0162] The tablets undergo an extended curing step (3 months) at 40° C. and 75% humidity to increase their hardness and to prevent their crushing by conventional techniques

(under a lighter or spoon) but also by less conventional but more efficient techniques (mortar, pliers or hammer for example).

[0163] The tablets thus hardened have a hardness greater than 500 N, which is equivalent to a crush resistance of more than 7.4 MPa. Under these conditions, release of the active ingredient is maintained with more than 90% of active ingredient released over 24 h as illustrated FIG. **3**.

EXAMPLE 4

Coated Alcohol-Resistant and pH-Independent Oxycodone Tablets

[0164] Coated, sustained-release, 40 mg oxycodone tablets are prepared (technical batch n° XCOX5111).

[0165] As in Example 1, the oxycodone is first granulated in a fluidised air bed (GPCG1) in the presence of water and a binding agent (HPMC 606).

4.1. Preparation of the Tablets

4.1.1. Preparation of the Compression Matrix

[0166] A pre-mixture of microcrystalline cellulose (Avicel® PH102, FMC) and precipitated silica (Syloïd® 244, Keyser & Mc Kay) is formed in a cubic mixer (AR 401, Erweka) for 2 min at 40 rpm. The polyvinylacetate/povidone mixture (80:20) (Kollidon® SR, BASF) and the oxycodone granules are added to the previous pre-mixture and homogenization is conducted in a cubic mixer for 15 minutes at 40 rpm. Finally, the lubricant (magnesium stearate, Quimdis) intended to limit adherence and compression friction is added to the previous mixture according to the mixing parameters: 3 minutes at 40 rpm.

[0167] The quantity of granules used is determined so as to manufacture tablets containing 40 mg oxycodone.

[0168] The proportions of each of the excipients are summarized in Table 12 below.

TABLE 12

		Batch number XCOX5111	
Ingredients	Function	Percentage [%]	Weight (mg/tablet)
Oxycodone HCl granules	Granulated active ingred.	20.25	45.56
Kollidon ® SR	Sustained-release agent	39.53	88.93
Avicel ® PH102	Sustained-release agent	39.53	88.93
Syloïd ® 244	Flow agent	0.20	0.45
Magnesium stearate	Lubricant	0.50	1.13
Total		100.00	225.00

4.1.2. Compression

[0169] The compression step of the final mixture obtained in the preceding step is conducted on a compression press (PR-12, Sviac) under a compression force of 35 kN using oblong punches whose sizes are given in the table below.

[0170] Compression is performed in conventional manner without either the mixture to be compressed or the compression tooling being subjected to a heating step, whether before or during the actual compression step.

[0171] The tablets containing 40 mg oxycodone obtained after this step have the following characteristics which are given in Table 13:

TABLE 13

Batch n° of tablets	XCOX5111
Weight (mg)	225
Size (mm)	11 × 5
Shape	oblong
Thickness (mm)	4.2
Surface area (mm^2)	55
Hardness (N)	350
Crush resistance (MPa)	5.2
Friability (%)	0.0

[0172] It is therefore ascertained that the tablets conforming to the invention have very high crush resistance, of more than 5 MPa.

[0173] Other tablets containing a dose of 20, 40 and 80 mg are produced using a different process: the oxycodone granules are prepared in a high shear granulator. The mixture to be compressed is prepared as described for Examples 1 and 2. The tablets are compressed on a SVIAC PR12 rotary compressor, using oblong punches of different sizes depending on the doses to be manufactured, under a compression force in the order of 10 to 15 kN.

[0174] Their physical characteristics are given in Table 14 below:

TABLE 14

Dose	Tablet weight	Size L × W × Thickn.	Hardness (Crush resistance)
20 mg	175 mg	11.0 × 5.0 × 3.8 mm	300 N (4.9 MPa)
40 mg	225 mg	11.0 × 5.0 × 4.2 mm	350 N (5.2 MPa)
80 mg	325 mg	13.0 × 6.0 × 4.5 mm	400 N (5.6 MPa)

[0175] The tablets thus manufactured all have excellent crush resistance, which is greater than 6 Mpa irrespective of their size, even though at no time during the process was it necessary to heat the constituents of the tablets or the compression tooling to increase their hardness and resistance.

[0176] The «bare» tablets containing 40 mg of active ingredient after the compression step are then coated with a coating intended to delay their release profile into the body.

4.1.3. Coating

[0177] Coating of the tablets is conducted in a perforated pan (Trislot).

[0178] Coating uses an aqueous dispersion of ethylcellulose (Aquacoat® ECD-30, FMC) the proportion of ethylcellulose representing 2.87 weight % of the total weight of the coated tablets.

[0179] A curing step of the coating film is carried out in an oven at 60° C. for 24 h.

[0180] The proportion of the different excipients and the general formula of the coated tablets obtained are given in Table 15 below.

TABLE 15

	Batch n° XCOX5112	
	Percentage	mg/tablet
Oxycodone (DV000165)	17.40	42.98
HPMC 606	1.20	2.97
Kollidon SR ®	36.32	89.73
Ayicel PH102	36.32	89.73
Magnesium stearate	0.46	1.13
HPMC 603	2.76	6.81
Simethicone 30% (vs)	0.01	0.02
Aquacoat ECD-30 (vs)	2.87	7.08
DBS	0.69	1.70
Micronised talc	1.35	3.34
Syloid 244FP	0.63	1.57
Total	100.00	247.06

[0181] Other uncoated tablets containing doses of 20, 40, 80 and 160 mg are also coated following the method described above.

[0182] Their physical characteristics observed after coating are given in Table 16 below:

TABLE 16

Dose	Tablet weight	Size L × W × Thickn.	Hardness (Crush resistance)
20 mg	175 mg	11 × 5 × 3.8 mm	440 N (7.3 MPa)
40 mg	225 mg	11 × 5 × 4.2 mm	500 N (7.4 MPa)
80 mg	325 mg	13 × 6 × 4.5 mm	570 N (6.5 MPa)
160 mg	575 mg	15 × 7 × 5.8 mm	800 N (6.3 MPa)

[0183] The tablets thus manufactured all have excellent crush resistance, which is greater than 6 MPa irrespective of their size.

2. Dissolution Curves with and without the Presence of Alcohol in the Dissolution Medium

[0184] Coated 40 mg tablets prepared according to Example 4.3 are tested in dissolution under two conditions:

[0185] a) 0.1 N HCl medium without ethanol

[0186] b) 0.1 N HCl medium with 40% ethanol

[0187] Les dissolution conditions are as follows: rotating paddle method, paddle rotating speed: 100 rpm, volume of medium: 900 mL, 1 tablet per vessel. The oxycodone is assayed by 225 nm UV spectrophotometry.

[0188] The results of the dissolution tests are given in FIG. **4**.

[0189] It is found that, despite the presence of alcohol in the dissolution medium, the tablets of the invention maintain a sustained-release dissolution profile.

3. Dissolution Curves in Relation to pH

[0190] 40 mg tablets prepared as described above in this example were also tested with respect to pH-independence i.e. their ability to maintain a constant release profile irrespective of the pH value of the dissolution medium.

[0191] Two experimental conditions were used:

Dissolution medium of pH 6.8

Dissolution medium of pH 1.2

[0192] The dissolution profiles obtained are given in FIG. **5**.

[0193] It is ascertained that irrespective of the acidity of the dissolution medium, the tablets conforming to the invention maintain a constant sustained-release profile.

[0194] These tablets can therefore be considered to be pH-independent, imparting thereto a particular advantage insofar as they can be used as vectors for any of type of active ingredient which is to be released over an extended time.

4.3. Stability Studies

4.3.1. Storage Stability

[0195] The coated tablets containing 40 mg oxycodone, obtained following the above-described method, are examined with regard to stability in order to determine their reaction to storage.

[0196] The tablets are stored for 6 months under accelerated stability conditions in accordance with ICH standards in force (45° C.; 75% humidity) in two types of packs: a) Al/Al aluminium blister pack, and b) HDPE bottles (high density polyethylene) in the presence of a desiccant.

[0197] The characteristics of the tablets after the storage period are summarized in Table 17 below:

TABLE 17

Packaging	Initial dose	Dose after storage mg/tablet	Impurities	Hardness	Proportion of water
Blister Al/Al	40 mg	40.9 CV 0.5%	0.17%	>500N	3.5%
HDPE bottles	20 mg	19.9 CV 3.5%	0.17%	440N	3.6%

4.3.2. Dissolution Profiles Obtained after a Storage Period.

[0198] These dissolution profiles are obtained under the following conditions: rotating paddle method, paddle rotating speed: 100 rpm, volume of the dissolution medium: 900 mL, pH 6.8.

[0199] These are given in FIGS. **6** and **7**.

[0200] It is found that not only is the quantity of active ingredient maintained over time, but also that the release profiles of the active ingredient and the extreme hardness of the tablets are maintained after a storage period of 6 months.

[0201] The tablets conforming to the invention are therefore stable and show a dissolution profile which is both pH-independent and independent of the presence (even strong presence) of alcohol in the dissolution medium.

4.4. Clinical Trials

[0202] The 40 mg tablets prepared in this example are also tested in vivo to determine the plasma profile of oxycodone in patients receiving said tablets.

[0203] A clinical trial (Algorithme, Canada, n° OXY/24018/001) was conducted in 12 healthy, fasting, male and female volunteers separated into two semi-groups. Each semi-group was successively given the two treatments (tablets of the invention and reference product) after an intermediate period without any treatment (wash-out period).

[0204] The reference product used in this trial was OxyContin®, a sustained-release oxycodone tablet taken twice a day, also containing a dose of 40 mg. (batch N° 121777, expiry date April 2007, Purdue).

[0205] The oxycodone plasma profiles obtained are given in FIG. **8** and the parameters are grouped together in following Tables 18 and 19:

TABLE 18

	Test (invention)		Reference	
Parameter	Mean	CV	Mean	CV
C_{max} (ng/mL)	34.412	20	53.129	25.0
T_{max} (heures)	10.0	16.6	3.00	34.3
AUC_t (ng h/mL)	667.109	16.9	611.848	21.9
AUC_∞ (ng h/mL)	679.846	17.1	614.960	21.7
$AUC_{t/\infty}$ (%)	98.17	1.7	99.48	0.3
K_{el} ($hours^{-1}$)	0.1154	24.0	0.1561	16.4
$T_{1/2\ el}$ (hours)	6.39	28.0	4.56	17.2

Note:
For T_{max} values it is the mean value which is indicated; CV: Coefficient of variation; K_{el}: elimination rate constant; $T_{1/2\ el}$: elimination half-life.

TABLE 19

		90% confidence interval	
Parameters	Ratio	Lower	Upper
Cmax	65	58	73
AUC_t	110	104	116
AUC_∞	111	105	118

[0206] Therefore, the plasma profiles obtained show that there is no loss of bio-availability of the active ingredient, despite a decrease in Cmax.

[0207] As a result, these matrix tablets containing oxycodone conforming to the invention show a plasma profile after once-a-day administration in man such that the ratio of their Cmax to the Cmax observed after administering OxyContin® extended release tablets having the same dosage, does not exceed 0.7.

[0208] Also, these matrix tablets containing oxycodone according to the invention, have a plasma profile after once-a-day administration in man, such that the ratio of the AUC∞ observed with these tablets to the AUC∞ value observed with OxyContin® extended release tablets having the same dosage, lies within the bioequivalence interval of 80 to 125%.

[0209] These results are particularly advantageous since they mean that the oxycodone is just as well absorbed by the body as the reference product but, since its maximum concentration is reduced by around 35% in the tablets of the invention, it affords a substantial reduction in the risks of adverse effects which occur with high plasma concentrations.

EXAMPLE 5

Tablets of Oxycodone and Naloxone

5.1. Preparation of the Tablets

[0210] Tablets conforming to the invention are prepared by associating two active ingredients: oxycodone and naloxone.

[0211] Naloxone is an opiate antagonist, which inhibits the activity of oxycodone if the tablet is tampered with for administration via injection. When the tablet is taken in usual manner (oral route), the naloxone does not exert its antagonist effect since it is rapidly metabolised when ingested by oral route. The ratio of oxycodone/naloxone base used here is 4:1.

[0212] The tablets are produced in the same manner as in Example 4 (granulation of oxycodone in a high shear granulator). They do not undergo any heat treatment either before, during or after compression.

[0213] The general formula of the tablets thus manufactured (batch XCOX 5731) is summarized in Table 20 below.

TABLE 20

Raw materials	Mg/tab	(%)
Granulated oxycodone	22.66	12.51
Naloxone $2HCl \cdot H_2O$	6.10	3.37
Kollidon SR ®	75.54	41.71
Avicel pH102 ®	75.54	41.71
Syloïd 244	0.367	0.20
Magnesium stearate	0.91	0.50
Total	181.1	100.0

After compression the tablets have the physical characteristics given in following Table 21.

TABLE 21

Description of tablet	Round, flat, white
Diameter	8 mm
Thickness	2.90 mm
Mean weight	175.8 mg
Hardness	315 N
Diametral resistance	8.6 Mpa

[0214] It is ascertained that, conforming to the invention, it is possible to produce tablets with very high crush resistance possibly containing two active ingredients, in particular one opioid agent and one antagonist agent blocking action of the latter in the event of administering of the tablet via intravenous route.

5.2. Dissolution Profiles

[0215] Dissolution tests are conducted, as in the preceding examples, under the following conditions: Type II paddle apparatus/100 rpm/medium pH 6.8/volume of dissolution medium: 900 mL/assay by continuous UV spectrophotometry at 225 nm/vessel width: 10 mm.

[0216] The profile is given FIG. **8**.

[0217] It is found that these ultra-hard tablets show a sustained-release profile (90% of the active ingredient released after 12 hours).

EXAMPLE 6

Tablets Containing Mineral Derivatives

6.1. Preparation of the Tablets

[0218] The aim of this test is to produce tablets conforming to the invention in which mineral excipients are used as chief ingredient of the compression matrix.

[0219] Tablets are prepared containing oxycodone and dicalcium phosphate dihydrate (Emcompress®) to replace the excipients of Kollidon SR® and Avicel PH 102® type used in the preceding examples.

[0220] The preparation method is identical to the one described in Example 1 (granulation of oxycodone then physical mixing with the powdered excipients of the compression mixture).

[0221] The general production formula for these tablets (batch XCOX 5723) containing a dose of 20 mg is given in following Table 22.

TABLE 22

Raw materials	Mg/tabl	(%)
Granulated oxycodone (XOXY 5634)	22.57	12.90
Emcompress ®	151.21	86.40
Syloïd 244FP	0.35	0.20
Magnesium stearate	0.88	0.50
Total	175.00	100.00

[0222] The mixture obtained is compressed as in Example 1.

[0223] The physical characteristics of the tablets after compression are given in following Table 23:

TABLE 23

Description of tablet	Round, flat, white
Diameter	6 mm
Thickness	3.16 mm
Mean weight	178.8 mg
Hardness	170 N
Diametral resistance	5.7 Mpa

[0224] It is ascertained once again that the crush resistance obtained is well above 4 MPa, even though no heating step of the mixture or of the compression tooling was necessary.

6.2. Dissolution Profile

[0225] The tablets so obtained are then placed in a dissolution medium.

[0226] The dissolution conditions are the following: Type II paddle apparatus; paddle rotating speed: 100 rpm; medium pH 6.8; volume of dissolution medium: 900 ml; continuous UV at 225 nm; vessel 10 mm.

[0227] The results are given in FIG. **9**.

[0228] It is found that the tablets conforming to the invention obtained using mineral excipients are able to release oxycodone over a relatively extended time period.

EXAMPLE 8

Drug Abuse Tests

8.1. Crush Tests

[0229] The objective of this example is to determine the difficulty in breaking or crushing and optionally obtaining a powder from the Oxycodone tablets conforming to the invention, compared with tablets of the reference oxycodone product (OxyContin®).

[0230] Four means were chosen to implement this step and placed in increasing order of difficulty:

[0231] knife (Opinel® pocket knife type)

[0232] coffee spoon

[0233] combination pliers

[0234] glass mortar and pestle (laboratory glassware)

[0235] Assessment of crushing difficulty was determined in relation to the hardness of the tablet.

[0236] The physical characteristics of the tested Oxycodone tablets are given in Table 24.

TABLE 24

Tested tablet	Thickns.	Size	Shape	Wt. (mg)	Hardness (N)	Crush resistance (MPa)
OxyContin ® 20 mg	3.43	Diameter 7.24 mm	Round pink	135.9	105	2.7
Invention (20 mg)	3.30	Length 11.0 mm Width 5.5 mm	Oblong white	175.9	467	8.8

[0237] The crush resistance of the reference tablets is 3.3 times less than that of the tablet of the invention.

[0238] The use of pliers allowed rough crushing of the tablets (pieces of 1 to 2 mm), both for the reference product and for the tablets of the invention.

[0239] After the rough crushing step using pliers, use of the laboratory mortar enabled a fine powder to be obtained in both cases. However, the use of the mortar on intact tablets conforming to the invention did not permit their crushing.

[0240] The crushing difficulty observed on each of the types of tablet in relation to the tool used is summarized in following Table 25:

TABLE 25

	Knife	Coffee spoon	Pliers	Mortar
OxyContin ® 20 mg	Easily cut, Chipping	Easy crushing	Easy crushing, chipping	Very easy crushing
Invention 20 mg	Difficult to cut, no crushing	Crushing impossible	Easy crushing, chipping	Crushing impossible (without prior cutting)

[0241] The reference OxyContin® product can be crushed fairly easily, irrespective of the means used. Since it has low hardness strength, it has a tendency to chip.

[0242] On the other hand, the tablet conforming to the invention can only be crushed with combination pliers; a knife only achieves cutting but no crushing. After cutting, the pieces can be ground in a mortar.

8.2. Dissolution Tests

[0243] A tablet cut in half using a knife, and a tablet roughly crushed using pliers are subjected to a dissolution test to analyse the impact of cutting and crushing on the dissolution profile, compared with an intact tablet. This test is conducted on batch XCOX 5726 prepared following Example 4, and on the OxyContin® reference product.

[0244] The dissolution method is as follows: continuous dissolution, dissolution medium pH 6.8, 900 ml of medium per vessel, rotating paddle method, paddle rotating speed: 100 rpm, dosage: 40 mg active ingredient per vessel, vessel thickness: 10 mm; measurement by UV spectrometry (wavelength λ=225 nm). Readings are taken every 5 minutes during the first hour, then every 15 minutes up to 24 h.

[0245] The results obtained for dissolutions in the pH 6.8 medium are given in following Table 26 and in FIG. **11**.

TABLE 26

	OxyContin ® 20 mg batch 122810			Oxycodone 20 mg XCOX 5726		
Time (h)	Whole tablet	Tablet cut in half	Tablet in pieces	Whole tablet	Tablet cut in half	Tablet in pieces
0.5	35.9	50.8	61.0	1.3	8.6	26.7
1	47.1	62.8	73.4	3.7	15.0	36.5
2	60.5	75.2	85.4	10.7	28.2	51.5
3	69.4	82.3	91.6	17.3	39.4	62.2
4	76.2	87.0	95.4	24.9	49.7	70.4
6	86.0	92.9	99.0	41.7	64.8	81.9
8	92.8	96.5	100.3	55.8	75.3	88.8
12	100.7	99.4	100.7	75.7	88.1	95.9
16	103.4	100.1	100.5	87.7	94.7	99.2
20	103.9	99.4	99.5	95.3	98.4	100.7
24	—	98.2	99.2	100.4	100.5	101.5

[0246] It is ascertained that in a pH 6.8 medium, the dissolution profile of the reference product is close to that targeted for the bare tablet i.e. without a sustained-release coating, whereas the profile of the tablet of the invention («QD») is close to that targeted for a sustained-release tablet.

[0247] The cutting in half of the tablet accelerates dissolution, and acceleration is increased when the tablet is cut in pieces for both types of tablets, making the active ingredient more rapidly available for absorption via oral route.

[0248] However, the profile of the oxycodone in the crushed «QD» tablet, conforming to the invention, remains a sustained-release profile.

8.3 Evaluation of Extraction of the Active Ingredient

[0249] The tested tablets are also evaluated regarding the extraction of their active ingredient for injection.

[0250] The applicant used the so-called «Stéribox®» kit available in pharmacies and designed for drug addicts, for the purpose of preventing the transmission of pathogenic agents through the exchange of contaminated syringes.

[0251] The Stéribox® contains:

[0252] two 1 ml syringes,

[0253] two 5 ml doses of water for injection preparations,

[0254] two cups so-called «Stéricup®»

[0255] two filters

[0256] Extraction of oxycodone from the reference product and from the tablet conforming to the invention is conducted as follows on each batch:

[0257] 2 tests on a whole tablet,

[0258] 2 tests on a tablet roughly crushed with pliers,

[0259] 2 tests on a tablet of the invention crushed with pliers and then with mortar and pestle, and

[0260] 2 tests on a reference tablet directly crushed in a mortar.

[0261] The tested extraction medium is the water supplied with the Stéribox®, in the maximum available volume (2 ml).

[0262] The operating mode used for extraction is the one described in the leaflet supplied with the Stéribox®:

[0263] 1 place the prepared sample (whole, roughly crushed or ground) in the cup,

[0264] 2—add 2 ml water using a gauged pipette,

[0265] 3—mix using the plunger of the syringe for 2 minutes,

[0266] 4—heat the content of the cup with a lighter for 1 minute,

[0267] 5—check the remaining volume after heating: the remaining volume is 1.7 ml.

[0268] 6—filter the solution using the sterile filter contained in the Steribox® and previously placed in the syringe. If necessary use a pipette to place the cup solution into the syringe,

[0269] 7—dilute the filtrate in water to obtain a theoretical concentration of active ingredient of 20 mg/100 ml

[0270] 8—conduct analysis replacing the extraction solvent by water for the reference product and the test product.

The results of the contents obtained and the extraction yields for each of the tests are summarized in following Table 27.

TABLE 27

	OxyContin 20 mg batch 122810			Oxycodone 20 mg XCOX 5726		
	Whole tablet	Roughly crushed tablet	Ground tablet	Whole tablet	Roughly crushed tablet	Ground tablet
Content obtained mg/tablet	0.37*	16.3	18.4	0.25	5.8	15.2
CV (%)	—	4.6	3.3	4.1	2.1	15.9
Yield	2.0%	86.2%	97.4%	1.3%	30.4%	79.6%

*The results concern a single test, the second test being cloudy and the result unusable.

[0271] It is found that the extraction yield is low with a whole tablet, irrespective of the tablet used.

[0272] However, extraction yields are higher for OxyContin® in all tests. In particular, when the tablet conforming to the invention is roughly crushed, it releases close to 5 times less active ingredient than the reference product used under the same conditions.

[0273] These results show that abuse by intravenous route can be achieved more easily with OxyContin® than with the oxycodone «QD» tablets of the invention.

[0274] Only pliers are required to obtain good extraction of OxyContin® whereas for the Oxycodone «QD» tablets of the invention an additional tool is required to achieve efficient crushing and thereby increase extraction yield. The tablets

conforming to the invention are therefore particularly effective to deter drug abuse of opioid active ingredients.

1. Water-insoluble, matrix tablets comprising oxycodone or one of its pharmaceutically acceptable salts, capable of releasing oxycodone into the body over an extended time period and comprising oxycodone within a compression matrix, said matrix comprising at least one excipient chosen from the group consisting of sustained-release, pH-independent, water-insoluble polymers, mineral excipients and their mixtures, wherein the quantity of excipient and the compression conditions are chosen so that the crush resistance of said tablets is at least 4 MPa, advantageously at least 6 MPa.

2. Matrix tablets according to claim **1**, wherein neither the mixture to be compressed, nor the compression tooling are subjected to a heating step either before or during the actual compression step.

3. Matrix tablets according to claim **1**, wherein said compression matrix represents 50 to 98 weight % of the total weight of said tablet, advantageously 85 to 95%.

4. Matrix tablets according to claim **1**, wherein said compression matrix comprises a mixture of at least two excipients selected from the group consisting of sustained-release, pH-independent, water-insoluble polymers, mineral excipients and their mixtures.

5. Matrix tablets according to claim **1**, wherein said sustained-release, pH-independent, water-insoluble polymers are selected from the group consisting of cellulose derivatives, water-insoluble methacrylic acids, derivatives of polyvinylalcohols, derivatives of polyvinyl acetates, derivatives of polyvinylpyrrolidone, lactic and glycolic acid polymers, starches, waxes and their mixtures.

6. Matrix tablets according to claim **1**, wherein the mineral excipients are selected from the group consisting of calcium phosphates, aluminium and silicon silicates, magnesium carbonate and their mixtures.

7. Matrix tablets according to claim **1**, wherein said polymers are selected from the group consisting of the mixture of microcrystalline cellulose and [polyvinyl acetate/polyvinylpyrrolidone (80:20)], and the mixture of microcrystalline cellulose and [poly(ethylacrylate/methylmethacrylate/trimethyl-amonioethyl methacrylate chloride) (1:2:0.2)].

8. Matrix tablets according to claim **1**, wherein said compression matrix also comprises at least one pharmaceutically acceptable excipient selected from the group consisting of anti-adherent agents, agents able to improve tablet cohesion on compressing, fillers, lubricants, plasticizers, bulking agents, sweeteners and colouring agents.

9. Matrix tablets according to claim **1**, wherein said compression matrix also comprises at least one or more of the following substances (a) to (f) or a mixture thereof:

a) a substance which irritates the nasal and/or pharyngeal tracts,

b) a viscosity-increasing agent, leading to formation of a gel when the tablet is dissolved in a minimum amount of water,

c) an emetic substance,

d) an aversive colouring agent,

e) a bittering substance,

f) an antagonist of oxycodone.

10. Matrix tablets according to claim **9**, wherein the antagonist agent is naloxone or naltrexone or one of their pharmaceutically acceptable salts.

11. Matrix tablets according to claim **1**, further comprising an outer coating.

12. Matrix tablets according to claim **11**, wherein said outer coating comprises at least one sustained-release polymer advantageously chosen from the group comprising ethylcellulose derivatives and methacrylic polymers.

13. Matrix tablets according to claim **1**, wherein said matrix comprises a mixture of microcrystalline cellulose and [polyvinyl acetate/polyvinylpyrrolidone (80:20)] to the proportion of (1:1).

14. Matrix tablets according to claim **13**, further comprising an outer coating comprising ethylcellulose.

15. Matrix tablets according to claim **1**, wherein said tablets are capable of releasing oxycodone over a period of more than 12 hours.

16. Matrix tablets according to claim **1**, wherein said tablets are capable of releasing oxycodone over a period of more than 20 hours.

17. Matrix tablets according to claim **13**, wherein said tablets have a plasma profile after once-a-day administration in man, such that the ratio of the Cmax observed after administration of said tablets to the Cmax value observed after administration of OxyContin® extended release tablets containing the same dose, does not exceed 0.7.

18. Matrix tablets containing oxycodone according to claim **13**, wherein a plasma profile after once-a-day administration in man is such that the ratio of AUC∞ observed for said tablets to the AUC∞ value observed with OxyContin® extended release tablets with the same dose, lies in the interval of 80 to 125%.

19. Tablets according to claim **1**, suitable for administration once a day.

20. Method to produce matrix tablets according to claim **1**, comprising the following steps:

mixing the active ingredient(s) with the excipient(s) of the compression matrix,

optional granulation, and

compressing said mixture under conditions chosen so that said tablet has a crush resistance of at least 4 MPa, advantageously at least 6 MPa.

21. Method according to claim **20**, wherein the compression step is conducted without the compression mixture or the compression tooling being subjected to a heating step either before or during the actual compression step.

22. Method according to claim **20**, further comprising coating said matrix tablet.

23. Method according to claim **22**, a further comprising curing said outer coating.

24. A method comprising administering a pharmaceutical composition in the form of tablets according to claim **1**, for the sustained delivery of oxycodone, and intended to prevent accidental misuse and/or to deter drug abuse of oxycodone.

* * * * *

EXHBIT B

1. PACKAGE INSERT

OXYCONTIN®

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS CII
10 mg 15 mg 20 mg 30 mg 40 mg 60 mg* 80 mg* 160 mg*

*** 60 mg, 80 mg, and 160 mg for use in opioid-tolerant patients only**

OT01343A

301371-0A

WARNING:

OxyContin is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

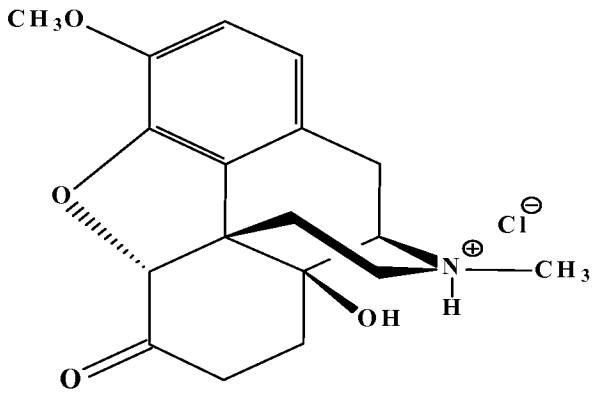
OxyContin Tablets are NOT intended for use as a prn analgesic.

OxyContin 60 mg, 80 mg, and 160 mg Tablets, or a single dose greater than 40 mg, ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. A single dose greater than 40 mg, or total daily doses greater than 80 mg, may cause fatal respiratory depression when administered to patients who are not tolerant to the respiratory depressant effects of opioids.

OxyContin TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OxyContin TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

DESCRIPTION

OxyContin® (oxycodone hydrochloride controlled-release) Tablets are an opioid analgesic supplied in 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, and 160 mg tablet strengths for oral administration. The tablet strengths describe the amount of oxycodone per tablet as the hydrochloride salt. The structural formula for oxycodone hydrochloride is as follows:



$C_{18}H_{21}NO_4 \bullet HCl$ MW 351.83

The chemical formula is 4, 5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride.

Oxycodone is a white, odorless crystalline powder derived from the opium alkaloid, thebaine. Oxycodone hydrochloride dissolves in water (1 g in 6 to 7 mL). It is slightly soluble in alcohol (octanol water partition coefficient 0.7). The tablets contain the following inactive ingredients: ammonio methacrylate copolymer, hypromellose, lactose, magnesium stearate, polyethylene glycol 400, povidone, sodium hydroxide, sorbic acid, stearyl alcohol, talc, titanium dioxide, and triacetin.

The 10 mg tablets also contain: hydroxypropyl cellulose.

The 15 mg tablets also contain: black iron oxide, yellow iron oxide, and red iron oxide.

The 20 mg tablets also contain: polysorbate 80 and red iron oxide.

The 30 mg tablets also contain: polysorbate 80, red iron oxide, yellow iron oxide, and black iron oxide.

The 40 mg tablets also contain: polysorbate 80 and yellow iron oxide.

The 60 mg tablets also contain: polysorbate 80 and FD&C Red No. 40 Aluminum Lake

The 80 mg tablets also contain: FD&C blue No. 2, hydroxypropyl cellulose, and yellow iron oxide.

The 160 mg tablets also contain: FD&C blue No. 2 and polysorbate 80.

CLINICAL PHARMACOLOGY

Oxycodone is a pure agonist opioid whose principal therapeutic action is analgesia. Other members of the class known as opioid agonists include substances such as morphine, hydromorphone, fentanyl, codeine, and hydrocodone. Pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, and cough suppression, as well as analgesia. Like all pure opioid agonist analgesics, with increasing doses there is increasing analgesia, unlike with mixed agonist/antagonists or non-opioid analgesics, where there is a limit to the analgesic effect with increasing doses. With pure opioid agonist analgesics, there is no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by side effects, the more serious of which may include somnolence and respiratory depression.

Central Nervous System

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug.

Oxycodone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension and to electrical stimulation.

Oxycodone depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Oxycodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of OxyContin® overdose (See **OVERDOSAGE**).

Gastrointestinal Tract And Other Smooth Muscle

Oxycodone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System

Oxycodone may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Concentration – Efficacy Relationships

Studies in normal volunteers and patients reveal predictable relationships between oxycodone dosage and plasma oxycodone concentrations, as well as between concentration and certain expected opioid effects, such as pupillary constriction, sedation, overall "drug effect", analgesia and feelings of "relaxation".

As with all opioids, the minimum effective plasma concentration for analgesia will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. As a result, patients must be treated with individualized titration of dosage to the desired effect. The minimum effective analgesic concentration of oxycodone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance.

Concentration – Adverse Experience Relationships

OxyContin® Tablets are associated with typical opioid-related adverse experiences. There is a general relationship between increasing oxycodone plasma concentration and increasing frequency of dose-related opioid adverse experiences such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation is altered by the development of tolerance to opioid-related side effects, and the relationship is not clinically relevant.

As with all opioids, the dose must be individualized (see **DOSAGE AND ADMINISTRATION**), because the effective analgesic dose for some patients will be too high to be tolerated by other patients.

PHARMACOKINETICS AND METABOLISM

The activity of OxyContin Tablets is primarily due to the parent drug oxycodone. OxyContin Tablets are designed to provide controlled delivery of oxycodone over 12 hours.

Breaking, chewing or crushing OxyContin Tablets eliminates the controlled delivery mechanism and results in the rapid release and absorption of a potentially fatal dose of oxycodone.

Oxycodone release from OxyContin Tablets is pH independent. Oxycodone is well absorbed from OxyContin Tablets with an oral bioavailability of 60% to 87%. The relative oral bioavailability of OxyContin to immediate-release oral dosage forms is 100%. Upon repeated dosing in normal volunteers in pharmacokinetic studies, steady-state levels were achieved within 24-36 hours. Dose proportionality and/or bioavailability has been established for the 10 mg, 20 mg, 40 mg, 80 mg, and 160 mg tablet strengths for both peak plasma levels (C_{max}) and extent of absorption (AUC). Oxycodone is extensively metabolized

and eliminated primarily in the urine as both conjugated and unconjugated metabolites. The apparent elimination half-life of oxycodone following the administration of OxyContin® was 4.5 hours compared to 3.2 hours for immediate-release oxycodone.

Absorption

About 60% to 87% of an oral dose of oxycodone reaches the central compartment in comparison to a parenteral dose. This high oral bioavailability is due to low pre-systemic and/or first-pass metabolism. In normal volunteers, the t½ of absorption is 0.4 hours for immediate-release oral oxycodone. In contrast, OxyContin Tablets exhibit a biphasic absorption pattern with two apparent absorption half-lives of 0.6 and 6.9 hours, which describes the initial release of oxycodone from the tablet followed by a prolonged release.

Plasma Oxycodone by Time

Dose proportionality has been established for the 10 mg, 20 mg, 40 mg, and 80 mg tablet strengths for both peak plasma concentrations (C_{max}) and extent of absorption (AUC) (see Table 1 below). Another study established that the 160 mg tablet is bioequivalent to 2 x 80 mg tablets as well as to 4 x 40 mg for both peak plasma concentrations (C_{max}) and extent of absorption (AUC) (see Table 2 below). Given the short half-life of elimination of oxycodone from OxyContin®, steady-state plasma concentrations of oxycodone are achieved within 24-36 hours of initiation of dosing with OxyContin Tablets. In a study comparing 10 mg of OxyContin every 12 hours to 5 mg of immediate-release oxycodone every 6 hours, the two treatments were found to be equivalent for AUC and C_{max}, and similar for C_{min} (trough) concentrations.

Plasma Oxycodone By Time

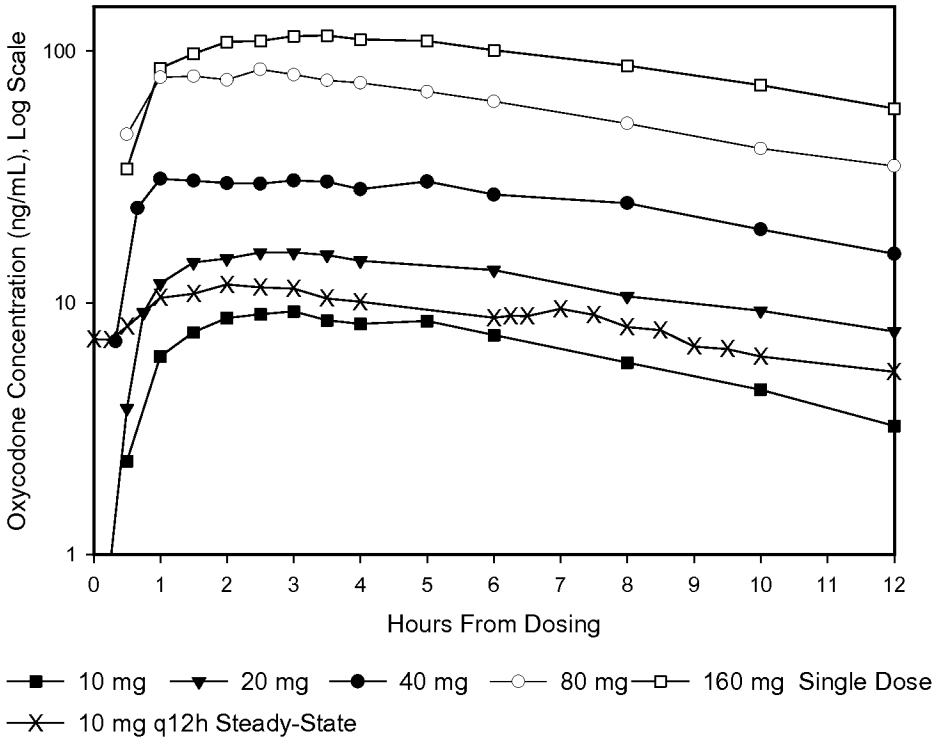


TABLE 1

Mean [% coefficient variation]

Regimen	Dosage Form	AUC (ng•hr/mL)†	C_{max} (ng/mL)	T_{max} (hrs)	Trough Conc. (ng/mL)
Single Dose	10 mg OxyContin	100.7 [26.6]	10.6 [20.1]	2.7 [44.1]	n.a.
	20 mg OxyContin	207.5 [35.9]	21.4 [36.6]	3.2 [57.9]	n.a.
	40 mg OxyContin	423.1 [33.3]	39.3 [34.0]	3.1 [77.4]	n.a.
	80 mg OxyContin*	1085.5 [32.3]	98.5 [32.1]	2.1 [52.3]	n.a.
Multiple Dose	10 mg OxyContin Tablets q12h	103.6 [38.6]	15.1 [31.0]	3.2 [69.5]	7.2 [48.1]
	5 mg immediate-release q6h	99.0 [36.2]	15.5 [28.8]	1.6 [49.7]	7.4 [50.9]

TABLE 2

Mean [% coefficient variation]

Regimen	Dosage Form	AUC_{∞} (ng•hr/mL)†	C_{max} (ng/mL)	T_{max} (hrs)	Trough Conc. (ng/mL)

Single Dose	4 x 40 mg OxyContin*	1935.3 [34.7]	152.0 [28.9]	2.56 [42.3]	n.a.
	2 x 80 mg OxyContin*	1859.3 [30.1]	153.4 [25.1]	2.78 [69.3]	n.a.
	1 x 160 mg OxyContin*	1856.4 [30.5]	156.4 [24.8]	2.54 [36.4]	n.a.

† for single-dose AUC = $AUC_{0\text{-}inf}$; for multiple-dose AUC = $AUC_{0\text{-}T}$
* data obtained while volunteers received naltrexone which can enhance absorption

OxyContin® is NOT INDICATED FOR RECTAL ADMINISTRATION. Data from a study involving 21 normal volunteers show that OxyContin Tablets administered per rectum resulted in an AUC 39% greater and a C_{max} 9% higher than tablets administered by mouth. Therefore, there is an increased risk of adverse events with rectal administration.

Food Effects

Food has no significant effect on the extent of absorption of oxycodone from OxyContin. However, the peak plasma concentration of oxycodone increased by 25% when a OxyContin 160 mg Tablet was administered with a high-fat meal.

Distribution

Following intravenous administration, the volume of distribution (Vss) for oxycodone was 2.6 L/kg. Oxycodone binding to plasma protein at 37°C and a pH of 7.4 was about 45%. Once absorbed, oxycodone is distributed to skeletal muscle, liver, intestinal tract, lungs, spleen, and brain. Oxycodone has been found in breast milk (see **PRECAUTIONS**).

Metabolism

Oxycodone hydrochloride is extensively metabolized to noroxycodone, oxymorphone, noroxymorphone, and their glucuronides. The major circulating metabolite is noroxycodone with an AUC ratio of 0.6 relative to that of oxycodone. Noroxycodone is reported to be a considerably weaker analgesic than oxycodone. Oxymorphone, although possessing analgesic activity, is present in the plasma only in low concentrations. The correlation between oxymorphone concentrations and opioid effects was much less than that seen with oxycodone plasma concentrations. The analgesic activity profile of other metabolites is not known.

The formation of oxymorphone and noroxycodone is mediated by cytochrome P450 2D6 and cytochrome P450 3A4, respectively. In addition, noroxymorphone formation is mediated by both cytochrome P450 2D6 and cytochrome P450 3A4. Therefore, the formation of these metabolites can, in theory, be affected by other drugs (see **Drug-Drug Interactions**).

Excretion

Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: free oxycodone up to 19%; conjugated oxycodone up to 50%; free oxymorphone 0%; conjugated oxymorphone ≤ 14%; both free and

conjugated noroxycodone have been found in the urine but not quantified. The total plasma clearance was 0.8 L/min for adults.

Special Populations

Elderly

The plasma concentrations of oxycodone are only nominally affected by age, being 15% greater in elderly as compared to young subjects.

Gender

Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis. The reason for this difference is unknown.

Renal Impairment

Data from a pharmacokinetic study involving 13 patients with mild to severe renal dysfunction (creatinine clearance <60 mL/min) show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, and AUC values for oxycodone, noroxycodone, and oxymorphone 60%, 50%, and 40% higher than normal subjects, respectively. This is accompanied by an increase in sedation but not by differences in respiratory rate, pupillary constriction, or several other measures of drug effect. There was an increase in t½ of elimination for oxycodone of only 1 hour (see **PRECAUTIONS**).

Hepatic Impairment

Data from a study involving 24 patients with mild to moderate hepatic dysfunction show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, than normal subjects. AUC values are 95% and 65% higher, respectively. Oxymorphone peak plasma concentrations and AUC values are lower by 30% and 40%. These differences are accompanied by increases in some, but not other, drug effects. The t½ elimination for oxycodone increased by 2.3 hours (see **PRECAUTIONS**).

Drug-Drug Interactions (see PRECAUTIONS)

Oxycodone is metabolized in part by cytochrome P450 2D6 and cytochrome P450 3A4 and in theory can be affected by other drugs.

Oxycodone is metabolized in part by cytochrome P450 2D6 to oxymorphone which represents less than 15% of the total administered dose. This route of elimination may be blocked by a variety of drugs (e.g., certain cardiovascular drugs including amiodarone and quinidine as well as polycyclic anti-depressants). However, in a study involving 10 subjects using quinidine, a known inhibitor of cytochrome P450 2D6, the pharmacodynamic effects of oxycodone were unchanged.

Pharmacodynamics

A single-dose, double-blind, placebo- and dose-controlled study was conducted using OxyContin® (10, 20, and 30 mg) in an analgesic pain model involving 182 patients with moderate to severe pain. Twenty and 30 mg of OxyContin were superior in reducing pain compared with placebo, and this difference was statistically significant. The onset of analgesic action with OxyContin occurred within 1 hour in most patients following oral administration.

CLINICAL TRIALS

A double-blind placebo-controlled, fixed-dose, parallel group, two-week study was conducted in 133 patients with chronic, moderate to severe pain, who were judged as having inadequate pain control with their current therapy. In this study, 20 mg OxyContin q12h but not 10 mg OxyContin q12h decreased pain compared with placebo, and this difference was statistically significant.

INDICATIONS AND USAGE

OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

OxyContin is **NOT** intended for use as a prn analgesic.

Physicians should individualize treatment in every case, initiating therapy at the appropriate point along a progression from non-opioid analgesics, such as non-steroidal anti-inflammatory drugs and acetaminophen to opioids in a plan of pain management such as outlined by the World Health Organization, the Agency for Healthcare Research and Quality (formerly known as the Agency for HealthCare Policy and Research), the Federation of State Medical Boards Model Guidelines, or the American Pain Society.

OxyContin is not indicated for pain in the immediate postoperative period (the first 12-24 hours following surgery), or if the pain is mild, or not expected to persist for an extended period of time. OxyContin is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (See American Pain Society guidelines.)

CONTRAINDICATIONS

OxyContin® is contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated. This includes patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment), and patients with acute or severe bronchial asthma or hypercarbia. OxyContin is contraindicated in any patient who has or is suspected of having paralytic ileus.

WARNINGS

OXYCONTIN TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OXYCONTIN TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

OxyContin 60 mg, 80 mg, and 160 mg Tablets, or a single dose greater than 40 mg, ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. A single dose greater than 40 mg, or total daily doses greater than 80 mg, may cause fatal respiratory depression when administered to patients who are not tolerant to the respiratory depressant effects of opioids.

Patients should be instructed against use by individuals other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death.

Misuse, Abuse and Diversion of Opioids

Oxycodone is an opioid agonist of the morphine-type. Such drugs are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

OxyContin has been reported as being abused by crushing, chewing, snorting, or injecting the dissolved product. These practices will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see **WARNINGS** and **DRUG ABUSE AND ADDICTION**).

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

Interactions with Alcohol and Drugs of Abuse

Oxycodone may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

DRUG ABUSE AND ADDICTION

OxyContin® contains oxycodone, which is a full mu-agonist opioid with an abuse liability similar to morphine and is a Schedule II controlled substance. Oxycodone, like morphine and other opioids used in analgesia, can be abused and is subject to criminal diversion.

Drug addiction is characterized by compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm. There is a potential for drug addiction to develop following exposure to opioids, including oxycodone. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common.

"Drug-seeking" behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated "loss" of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. OxyContin, like other opioids, has been diverted for non-medical use. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

OxyContin consists of a dual-polymer matrix, intended for oral use only. Abuse of the crushed tablet poses a hazard of overdose and death. This risk is increased with concurrent abuse of alcohol and other substances. With parenteral abuse, the tablet excipients, especially talc, can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Respiratory Depression

Respiratory depression is the chief hazard from oxycodone, the active ingredient in OxyContin®, as with all opioid agonists. Respiratory depression is a particular problem in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Oxycodone should be used with extreme caution in patients with significant chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression. In such patients, even usual therapeutic doses of oxycodone may decrease respiratory drive to the point of apnea. In these patients alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose.

Head Injury

The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in the presence of head injury, intracranial lesions, or other sources of pre-existing increased intracranial pressure. Oxycodone produces effects on pupillary response and consciousness which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries.

Hypotensive Effect

OxyContin may cause severe hypotension. There is an added risk to individuals whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. Oxycodone may produce orthostatic hypotension in ambulatory patients. Oxycodone, like all opioid analgesics of the morphine-type, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

PRECAUTIONS

General

Opioid analgesics have a narrow therapeutic index in certain patient populations, especially when combined with CNS depressant drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known risks of respiratory depression, altered mental state, and postural hypotension.

Use of OxyContin® is associated with increased potential risks and should be used only with caution in the following conditions: acute alcoholism; adrenocortical insufficiency (e.g., Addison's disease); CNS depression or coma; delirium tremens; debilitated patients; kyphoscoliosis associated with respiratory depression; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture; severe impairment of hepatic, pulmonary or renal function; and toxic psychosis.

The administration of oxycodone may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Oxycodone may aggravate convulsions in patients with convulsive disorders, and all opioids may induce or aggravate seizures in some clinical settings.

Interactions with other CNS Depressants

OxyContin should be used with caution and started in a reduced dosage (1/3 to 1/2 of the usual dosage) in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, other tranquilizers, and alcohol. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with the usual doses of OxyContin.

Interactions with Mixed Agonist/Antagonist Opioid Analgesics

Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as oxycodone. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and/or may precipitate withdrawal symptoms in these patients.

Ambulatory Surgery and Postoperative Use

OxyContin is not indicated for pre-emptive analgesia (administration pre-operatively for the management of postoperative pain).

OxyContin is not indicated for pain in the immediate postoperative period (the first 12 to 24 hours following surgery) for patients not previously taking the drug, because its safety in this setting has not been established.

OxyContin is not indicated for pain in the postoperative period if the pain is mild or not expected to persist for an extended period of time.

OxyContin is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate (See American Pain Society guidelines).

Patients who are already receiving OxyContin® Tablets as part of ongoing analgesic therapy may be safely continued on the drug if appropriate dosage adjustments are made considering the procedure, other drugs given, and the temporary changes in physiology caused by the surgical intervention (see **DOSAGE AND ADMINISTRATION**).

OxyContin and other morphine-like opioids have been shown to decrease bowel motility. Ileus is a common postoperative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in postoperative patients receiving opioids. Standard supportive therapy should be implemented.

Use in Pancreatic/Biliary Tract Disease

Oxycodone may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids like oxycodone may cause increases in the serum amylase level.

Tolerance and Physical Dependence

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or

upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid therapy.

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

In general, opioids should not be abruptly discontinued (see **DOSAGE AND ADMINISTRATION: Cessation of Therapy**).

Information for Patients/Caregivers

If clinically advisable, patients receiving OxyContin Tablets or their caregivers should be given the following information by the physician, nurse, pharmacist, or caregiver:

1. Patients should be aware that OxyContin Tablets contain oxycodone, which is a morphine-like substance.

2. Patients should be advised that OxyContin Tablets were designed to work properly only if swallowed whole. OxyContin Tablets will release all their contents at once if broken, chewed, or crushed, resulting in a risk of fatal overdose.

3. Patients should be advised to report episodes of breakthrough pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.

4. Patients should be advised not to adjust the dose of OxyContin® without consulting the prescribing professional.

5. Patients should be advised that OxyContin may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating heavy machinery).

6. Patients should not combine OxyContin with alcohol or other central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, because dangerous additive effects may occur, resulting in serious injury or death.

7. Women of childbearing potential who become, or are planning to become, pregnant should be advised to consult their physician regarding the effects of analgesics and other drug use during pregnancy on themselves and their unborn child.

8. Patients should be advised that OxyContin is a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.

9. Patients should be advised that they may pass empty matrix "ghosts" (tablets) via colostomy or in the stool, and that this is of no concern since the active medication has already been absorbed.

10. Patients should be advised that if they have been receiving treatment with OxyContin for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper the OxyContin dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. Their physician can provide a dose schedule to accomplish a gradual discontinuation of the medication.

11. Patients should be instructed to keep OxyContin in a secure place out of the reach of children. When OxyContin is no longer needed, the unused tablets should be destroyed by flushing down the toilet.

Use in Drug and Alcohol Addiction

OxyContin is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission is for the management of pain requiring opioid analgesia.

Drug-Drug Interactions

Opioid analgesics, including OxyContin®, may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Oxycodone is metabolized in part by cytochrome P450 2D6 and cytochrome P450 3A4 and in theory can be affected by other drugs.

Oxycodone is metabolized in part to oxymorphone via cytochrome P450 2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs including amiodarone and quinidine as well as polycyclic antidepressants), such blockade has not yet been shown to be of clinical significance with this agent. Clinicians should be aware of this possible interaction, however.

Use with CNS Depressants

OxyContin, like all opioid analgesics, should be started at 1/3 to 1/2 of the usual dosage in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, centrally acting anti-emetics, tranquilizers, and alcohol because respiratory depression, hypotension, and profound sedation or coma may result. No specific interaction between oxycodone and monoamine oxidase inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies of oxycodone to evaluate its carcinogenic potential have not been conducted.

Oxycodone was not mutagenic in the following assays: Ames Salmonella and E. coli test with and without metabolic activation at doses of up to 5000 μg, chromosomal aberration test in human lymphocytes in the absence of metabolic activation at doses of up to 1500 μg/mL and with activation 48 hours after exposure at doses of up to 5000 μg/mL, and in the in vivo bone marrow micronucleus test in mice (at plasma levels of up to 48 μg/mL). Oxycodone was clastogenic in the human lymphocyte chromosomal assay in the presence of metabolic activation in the human chromosomal aberration test (at greater than or equal to 1250 μg/mL) at 24 but not 48 hours of exposure and in the mouse lymphoma assay at doses of 50 μg/mL or greater with metabolic activation and at 400 μg/mL or greater without metabolic activation.

Pregnancy

Teratogenic Effects - Category B: Reproduction studies have been performed in rats and rabbits by oral administration at doses up to 8 mg/kg and 125 mg/kg, respectively. These doses are 3 and 46 times a human dose of 160 mg/day, based on mg/kg basis. The results did not reveal evidence of harm to the fetus due to oxycodone. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

OxyContin® is not recommended for use in women during and immediately prior to labor and delivery because oral opioids may cause respiratory depression in the newborn. Neonates whose mothers have been taking oxycodone chronically may exhibit respiratory depression and/or withdrawal symptoms, either at birth and/or in the nursery.

Nursing Mothers

Low concentrations of oxycodone have been detected in breast milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of an opioid analgesic is stopped. Ordinarily, nursing should not be undertaken while a patient is receiving OxyContin because of the possibility of sedation and/or respiratory depression in the infant.

Pediatric Use

Safety and effectiveness of OxyContin have not been established in pediatric patients below the age of 18. **It must be remembered that OxyContin Tablets cannot be crushed or divided for administration.**

Geriatric Use

In controlled pharmacokinetic studies in elderly subjects (greater than 65 years) the clearance of oxycodone appeared to be slightly reduced. Compared to young adults, the plasma concentrations of oxycodone were increased approximately 15% (see **PHARMACOKINETICS AND METABOLISM**). Of the total number of subjects (445) in clinical studies of OxyContin, 148 (33.3%) were age 65 and older (including those age 75 and older) while 40 (9.0%) were age 75 and older. In clinical trials with appropriate initiation of therapy and dose titration, no untoward or unexpected side effects were seen in

the elderly patients who received OxyContin. Thus, the usual doses and dosing intervals are appropriate for these patients. As with all opioids, the starting dose should be reduced to 1/3 to 1/2 of the usual dosage in debilitated, non-tolerant patients. Respiratory depression is the chief hazard in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Laboratory Monitoring

Due to the broad range of plasma concentrations seen in clinical populations, the varying degrees of pain, and the development of tolerance, plasma oxycodone measurements are usually not helpful in clinical management. Plasma concentrations of the active drug substance may be of value in selected, unusual or complex cases.

Hepatic Impairment

A study of OxyContin in patients with hepatic impairment indicates greater plasma concentrations than those with normal function. The initiation of therapy at 1/3 to 1/2 the usual doses and careful dose titration is warranted.

Renal Impairment

In patients with renal impairment, as evidenced by decreased creatinine clearance (<60 mL/min), the concentrations of oxycodone in the plasma are approximately 50% higher than in subjects with normal renal function. Dose initiation should follow a conservative approach. Dosages should be adjusted according to the clinical situation.

Gender Differences

In pharmacokinetic studies, opioid-naive females demonstrate up to 25% higher average plasma concentrations and greater frequency of typical opioid adverse events than males, even after adjustment for body weight. The clinical relevance of a difference of this magnitude is low for a drug intended for chronic usage at individualized dosages, and there was no male/female difference detected for efficacy or adverse events in clinical trials.

ADVERSE REACTIONS

The safety of OxyContin® was evaluated in double-blind clinical trials involving 713 patients with moderate to severe pain of various etiologies. In open-label studies of cancer pain, 187 patients received OxyContin in total daily doses ranging from 20 mg to 640 mg per day. The average total daily dose was approximately 105 mg per day.

Serious adverse reactions which may be associated with OxyContin Tablet therapy in clinical use are those observed with other opioid analgesics, including respiratory depression, apnea, respiratory arrest, and (to an even lesser degree) circulatory depression, hypotension, or shock (see **OVERDOSAGE**).

The non-serious adverse events seen on initiation of therapy with OxyContin are typical opioid side effects. These events are dose-dependent, and their frequency depends upon the

dose, the clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual. They should be expected and managed as a part of opioid analgesia. The most frequent (>5%) include: constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and asthenia.

In many cases the frequency of these events during initiation of therapy may be minimized by careful individualization of starting dosage, slow titration, and the avoidance of large swings in the plasma concentrations of the opioid. Many of these adverse events will cease or decrease in intensity as OxyContin therapy is continued and some degree of tolerance is developed.

Clinical trials comparing OxyContin with immediate-release oxycodone and placebo revealed a similar adverse event profile between OxyContin and immediate-release oxycodone. The most common adverse events (>5%) reported by patients at least once during therapy were:

TABLE 3

	OxyContin (n=227)	**Immediate-Release (n=225)**	**Placebo (n=45)**
	(%)	**(%)**	**(%)**
Constipation	(23)	(26)	(7)
Nausea	(23)	(27)	(11)
Somnolence	(23)	(24)	(4)
Dizziness	(13)	(16)	(9)
Pruritus	(13)	(12)	(2)
Vomiting	(12)	(14)	(7)
Headache	(7)	(8)	(7)
Dry Mouth	(6)	(7)	(2)
Asthenia	(6)	(7)	-
Sweating	(5)	(6)	(2)

The following adverse experiences were reported in OxyContin®-treated patients with an incidence between 1% and 5%. In descending order of frequency they were anorexia, nervousness, insomnia, fever, confusion, diarrhea, abdominal pain, dyspepsia, rash, anxiety, euphoria, dyspnea, postural hypotension, chills, twitching, gastritis, abnormal dreams, thought abnormalities, and hiccups.

The following adverse reactions occurred in less than 1% of patients involved in clinical trials or were reported in postmarketing experience.

Blood and lymphatic system disorders: lymphadenopathy

Cardiac disorders: palpitations (in the context of withdrawal)

Ear and labyrinth disorders: tinnitus

Endocrine disorders: syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Eye disorders: abnormal vision

Gastrointestinal disorders: dysphagia, eructation, flatulence, gastrointestinal disorder, ileus, increased appetite, stomatitis

General disorders and administration site conditions: chest pain, edema, facial edema, malaise, pain, peripheral edema, thirst, withdrawal syndrome (with and without seizures)

Immune system disorders: anaphylactic or anaphylactoid reaction (symptoms of)

Infections and infestations: pharyngitis

Injury, poisoning and procedural complications: accidental injury

Investigations: hyponatremia, increased hepatic enzymes, ST depression

Metabolism and nutrition disorders: dehydration

Musculoskeletal and connective tissue disorders: neck pain

Nervous system disorders: abnormal gait, amnesia, hyperkinesia, hypertonia (muscular), hypesthesia, hypotonia, migraine, paresthesia, seizures, speech disorder, stupor, syncope, taste perversion, tremor, vertigo

Psychiatric disorders: agitation, depersonalization, depression, emotional lability, hallucination

Renal and urinary disorders: dysuria, hematuria, polyuria, urinary retention, urination impaired

Reproductive system and breast disorders: amenorrhea, decreased libido, impotence

Respiratory, thoracic and mediastinal disorders: cough increased, voice alteration

Skin and subcutaneous tissue disorders: dry skin, exfoliative dermatitis, urticaria

Vascular disorders: vasodilation

OVERDOSAGE

Acute overdosage with oxycodone can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, and death.

Deaths due to overdose have been reported with abuse and misuse of OxyContin®, by ingesting, inhaling, or injecting the crushed tablets. Review of case reports has indicated that the risk of fatal overdose is further increased when OxyContin is abused concurrently with alcohol or other CNS depressants, including other opioids.

In the treatment of oxycodone overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

The pure opioid antagonists such as naloxone or nalmefene are specific antidotes against respiratory depression from opioid overdose. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose. In patients who are physically dependent on any opioid agonist including OxyContin, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. Please see the prescribing information for the specific opioid antagonist for details of their proper use.

DOSAGE AND ADMINISTRATION

General Principles

OXYCONTIN IS AN OPIOID AGONIST AND A SCHEDULE II CONTROLLED SUBSTANCE WITH AN ABUSE LIABILITY SIMILAR TO MORPHINE. OXYCODONE, LIKE MORPHINE AND OTHER OPIOIDS USED IN ANALGESIA, CAN BE ABUSED AND IS SUBJECT TO CRIMINAL DIVERSION.

OXYCONTIN TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OXYCONTIN® TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

One OxyContin 160 mg tablet is comparable to two 80 mg tablets when taken on an empty stomach. With a high-fat meal, however, there is a 25% greater peak plasma concentration following one 160 mg tablet. Dietary caution should be taken when patients are initially titrated to 160 mg tablets (see DOSAGE AND ADMINISTRATION).

Patients should be started on the lowest appropriate dose (see **DOSAGE AND ADMINISTRATION: Initiation of Therapy**). In treating pain it is vital to assess the patient regularly and systematically. Therapy should also be regularly reviewed and adjusted based upon the patient's own reports of pain and side effects and the health professional's clinical judgment.

OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time. The controlled-release nature of the formulation allows OxyContin to be effectively administered every 12 hours (see **CLINICAL PHARMACOLOGY; PHARMACOKINETICS AND METABOLISM**). While symmetric (same dose AM and PM), around-the-clock, q12h dosing is appropriate for the majority of patients, some patients may benefit from asymmetric (different dose given in AM than in PM) dosing, tailored to their pain pattern. It is usually appropriate to treat a patient with only one opioid for around-the-clock therapy.

Physicians should individualize treatment using a progressive plan of pain management such as outlined by the World Health Organization, the American Pain Society and the Federation of State Medical Boards Model Guidelines. Healthcare professionals should follow appropriate pain management principles of careful assessment and ongoing monitoring (see **BOXED WARNING**).

Initiation of Therapy

It is critical to initiate the dosing regimen for each patient individually, taking into account the patient's prior opioid and non-opioid analgesic treatment. Attention should be given to:

(1) the general condition and medical status of the patient;
(2) the daily dose, potency, and kind of the analgesic(s) the patient has been taking;
(3) the reliability of the conversion estimate used to calculate the dose of oxycodone;
(4) the patient's opioid exposure and opioid tolerance (if any);
(5) the **Special Instructions for OxyContin 60 mg, 80 mg, and 160 mg Tablets, or a Single Dose Greater Than 40 mg**; and
(6) the balance between pain control and adverse experiences.

Care should be taken to use low initial doses of OxyContin in patients who are not already opioid-tolerant, especially those who are receiving concurrent treatment with muscle relaxants, sedatives, or other CNS active medications (see **PRECAUTIONS: Drug-Drug Interactions**).

For initiation of OxyContin therapy for patients previously taking opioids, the conversion ratios from Foley, KM. [NEJM, 1985; 313:84-95], found below, are a reasonable starting point, although not verified in well-controlled, multiple-dose trials.

Experience indicates a reasonable starting dose of OxyContin for patients who are taking non-opioid analgesics and require continuous around-the-clock therapy for an extended period of time is 10 mg q12h. If a non-opioid analgesic is being provided, it may be continued. OxyContin should be individually titrated to a dose that provides adequate analgesia and minimizes side effects.

1. Using standard conversion ratio estimates (see Table 4 below), multiply the mg/day of the previous opioids by the appropriate multiplication factors to obtain the equivalent total daily dose of oral oxycodone.

2. When converting from oxycodone, divide the 24-hour oxycodone dose in half to obtain the twice a day (q12h) dose of OxyContin.

3. Round down to a dose which is appropriate for the tablet strengths available.

4. Discontinue all other around-the-clock opioid drugs when OxyContin therapy is initiated.

5. No fixed conversion ratio is likely to be satisfactory in all patients, especially patients receiving large opioid doses. The recommended doses shown in Table 4 are only a starting point, and close observation and frequent titration are indicated until patients are stable on the new therapy.

TABLE 4.

Multiplication Factors for Converting the Daily Dose of Prior Opioids to the Daily Dose of Oral Oxycodone*

	(Mg/Day Prior Opioid x Factor = Mg/Day Oral Oxycodone)	
	Oral Prior Opioid	**Parenteral Prior Opioid**
Oxycodone	1	--
Codeine	0.15	--
Hydrocodone	0.9	--
Hydromorphone	4	20
Levorphanol	7.5	15
Meperidine	0.1	0.4
Methadone	1.5	3
Morphine	0.5	3

* **To be used only for conversion to oral oxycodone**. For patients receiving high-dose parenteral opioids, a more conservative conversion is warranted. For example, for high-dose parenteral morphine, use 1.5 instead of 3 as a multiplication factor.

In all cases, supplemental analgesia should be made available in the form of a suitable short-acting analgesic.

OxyContin® can be safely used concomitantly with usual doses of non-opioid analgesics and analgesic adjuvants, provided care is taken to select a proper initial dose (see **PRECAUTIONS**).

Conversion from Transdermal Fentanyl to OxyContin

Eighteen hours following the removal of the transdermal fentanyl patch, OxyContin treatment can be initiated. Although there has been no systematic assessment of such conversion, a conservative oxycodone dose, approximately 10 mg q12h of OxyContin, should be initially substituted for each 25 µg/hr fentanyl transdermal patch. The patient should be followed closely for early titration, as there is very limited clinical experience with this conversion.

Managing Expected Opioid Adverse Experiences

Most patients receiving opioids, especially those who are opioid-naive, will experience side effects. Frequently the side effects from OxyContin are transient, but may require evaluation and management. Adverse events such as constipation should be anticipated and treated aggressively and prophylactically with a stimulant laxative and/or stool softener. Patients do not usually become tolerant to the constipating effects of opioids.

Other opioid-related side effects such as sedation and nausea are usually self-limited and often do not persist beyond the first few days. If nausea persists and is unacceptable to the

patient, treatment with antiemetics or other modalities may relieve these symptoms and should be considered.

Patients receiving OxyContin® may pass an intact matrix "ghost" in the stool or via colostomy. These ghosts contain little or no residual oxycodone and are of no clinical consequence.

Individualization of Dosage

Once therapy is initiated, pain relief and other opioid effects should be frequently assessed. Patients should be titrated to adequate effect (generally mild or no pain with the regular use of no more than two doses of supplemental analgesia per 24 hours). Patients who experience breakthrough pain may require dosage adjustment or rescue medication. Because steady-state plasma concentrations are approximated within 24 to 36 hours, dosage adjustment may be carried out every 1 to 2 days. It is most appropriate to increase the q12h dose, not the dosing frequency. There is no clinical information on dosing intervals shorter than q12h. As a guideline, the total daily oxycodone dose usually can be increased by 25% to 50% of the current dose at each increase.

If signs of excessive opioid-related adverse experiences are observed, the next dose may be reduced. If this adjustment leads to inadequate analgesia, a supplemental dose of immediate-release oxycodone may be given. Alternatively, non-opioid analgesic adjuvants may be employed. Dose adjustments should be made to obtain an appropriate balance between pain relief and opioid-related adverse experiences.

If significant adverse events occur before the therapeutic goal of mild or no pain is achieved, the events should be treated aggressively. Once adverse events are under control, upward titration should continue to an acceptable level of pain control.

During periods of changing analgesic requirements, including initial titration, frequent contact is recommended between physician, other members of the healthcare team, the patient and the caregiver/family.

Special Instructions for OxyContin 60 mg, 80 mg, and 160 mg Tablets, or a Single Dose Greater Than 40 mg (for use in opioid-tolerant patients only)

OxyContin 60 mg, 80 mg, and 160 mg Tablets, or a single dose greater than 40 mg, are for use in opioid-tolerant patients only. A single daily dose greater than 40 mg, or total daily doses greater than 80 mg, may cause fatal respiratory depression when administered to patients who are not tolerant to the respiratory depressant effects of opioids. Patients should be instructed against use by individuals other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death.

One OxyContin® 160 mg tablet is comparable to two 80 mg tablets when taken on an empty stomach. With a high-fat meal, however, there is a 25% greater peak plasma

concentration following one 160 mg tablet. Dietary caution should be taken when patients are initially titrated to 160 mg tablets.

Supplemental Analgesia

Most patients given around-the-clock therapy with controlled-release opioids may need to have immediate-release medication available for exacerbations of pain or to prevent pain that occurs predictably during certain patient activities (incident pain).

Maintenance of Therapy

The intent of the titration period is to establish a patient-specific q12h dose that will maintain adequate analgesia with acceptable side effects for as long as pain relief is necessary. Should pain recur then the dose can be incrementally increased to re-establish pain control. The method of therapy adjustment outlined above should be employed to re-establish pain control.

During chronic therapy, especially for non-cancer pain syndromes, the continued need for around-the-clock opioid therapy should be reassessed periodically (e.g., every 6 to 12 months) as appropriate.

Cessation of Therapy

When the patient no longer requires therapy with OxyContin Tablets, doses should be tapered gradually to prevent signs and symptoms of withdrawal in the physically dependent patient.

Conversion from OxyContin to Parenteral Opioids

To avoid overdose, conservative dose conversion ratios should be followed.

SAFETY AND HANDLING

OxyContin Tablets are solid dosage forms that contain oxycodone, which is a controlled substance. Like morphine, oxycodone is controlled under Schedule II of the Controlled Substances Act.

OxyContin has been targeted for theft and diversion by criminals. Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

HOW SUPPLIED

OxyContin® (oxycodone hydrochloride controlled-release) Tablets 10 mg are round, unscored, white-colored, convex tablets imprinted with OC on one side and 10 on the other. They are supplied as follows:

NDC 59011-100-10: child-resistant closure, opaque plastic bottles of 100
NDC 59011-100-20: unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton

OxyContin® (oxycodone hydrochloride controlled-release) Tablets 15 mg are round, unscored, gray-colored, convex tablets imprinted with OC on one side and 15 on the other. They are supplied as follows:

NDC 59011-815-10: child-resistant closure, opaque plastic bottles of 100

OxyContin® (oxycodone hydrochloride controlled-release) Tablets 20 mg are round, unscored, pink-colored, convex tablets imprinted with OC on one side and 20 on the other. They are supplied as follows:

NDC 59011-103-10: child-resistant closure, opaque plastic bottles of 100
NDC 59011-103-20: unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton

OxyContin® (oxycodone hydrochloride controlled-release) Tablets 30 mg are round, unscored, brown-colored, convex tablets imprinted with OC on one side and 30 on the other. They are supplied as follows:

NDC 59011-830-10: child-resistant closure, opaque plastic bottles of 100

OxyContin® (oxycodone hydrochloride controlled-release) Tablets 40 mg are round, unscored, yellow-colored, convex tablets imprinted with OC on one side and 40 on the other. They are supplied as follows:

NDC 59011-105-10: child-resistant closure, opaque plastic bottles of 100
NDC 59011-105-20: unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton

OxyContin® (oxycodone hydrochloride controlled-release) Tablets 60 mg are round, unscored red-colored, convex tablets imprinted with OC on one side and 60 on the other. They are supplied as follows:

NDC 59011-860-10: child-resistant closure, opaque plastic bottles of 100

OxyContin® (oxycodone hydrochloride controlled-release) Tablets 80 mg are round, unscored, green-colored, convex tablets imprinted with OC on one side and 80 on the other. They are supplied as follows:

NDC 59011-107-10: child-resistant closure, opaque plastic bottles of 100
NDC 59011-107-20: unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton

OxyContin® (oxycodone hydrochloride controlled-release) Tablets 160 mg are caplet-shaped, unscored, blue-colored, convex tablets imprinted with OC on one side and 160 on the other. They are supplied as follows:

NDC 59011-109-10: child-resistant closure, opaque plastic bottles of 100
NDC 59011-109-20: unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton

Store at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F).

Dispense in tight, light-resistant container.

Healthcare professionals can telephone Purdue Pharma's Medical Services Department (1-888-726-7535) for information on this product.

CAUTION

DEA Order Form Required.

Purdue Pharma L.P.
Stamford, CT 06901-3431

U.S. Patent Numbers 5,508,042 and 7,129,248

November 5, 2007

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301371-0A

PATIENT INFORMATION

OXYCONTIN® CII
(Oxycodone HCl Controlled-Release) Tablets

OxyContin® Tablets, 10 mg
OxyContin® Tablets, 15 mg
OxyContin® Tablets, 20 mg
OxyContin® Tablets, 30 mg
OxyContin® Tablets, 40 mg
OxyContin® Tablets, 60 mg
OxyContin® Tablets, 80 mg
OxyContin® Tablets, 160 mg

Read this information carefully before you take OxyContin® (ox-e-CON-tin) tablets. Also read the information you get with your refills. There may be something new. This information does not take the place of talking with your doctor about your medical condition or your treatment. Only you and your doctor can decide if OxyContin is right for you. Share the important information in this leaflet with members of your household.

What Is The Most Important Information I Should Know About OxyContin®?

- **Use OxyContin the way your doctor tells you to.**
- **Use OxyContin only for the condition for which it was prescribed**.
- **OxyContin is not for occasional ("as needed") use.**
- **Swallow the tablets whole**. Do not break, crush, dissolve, or chew them before swallowing. OxyContin® works properly over 12 hours only when swallowed whole. **If a tablet is broken, crushed, dissolved, or chewed, the entire 12 hour dose will be absorbed into your body all at once. This can be dangerous, causing an overdose, and possibly death.**
- **Keep OxyContin® out of the reach of children.** Accidental overdose by a child is dangerous and may result in death.
- **Prevent theft and misuse.** OxyContin contains a narcotic painkiller that can be a target for people who abuse prescription medicines. Therefore, keep your tablets in a secure place, to protect them from theft. Never give them to anyone else. Selling or giving away this medicine is dangerous and against the law.

What is OxyContin®?

OxyContin® is a tablet that comes in several strengths and contains the medicine oxycodone (ox-e-KOE-done). This medicine is a painkiller like morphine. OxyContin treats moderate to severe pain that is expected to last for an extended period of time. Use OxyContin regularly during treatment. It contains enough medicine to last for up to twelve hours.

Who Should Not Take OxyContin®?

Do not take OxyContin® if

- your doctor did not prescribe OxyContin® for you.
- your pain is mild or will go away in a few days.
- your pain can be controlled by occasional use of other painkillers.
- you have severe asthma or severe lung problems.

- you have had a severe allergic reaction to codeine, hydrocodone, dihydrocodeine, or oxycodone (such as Tylox, Tylenol with Codeine, or Vicodin). A severe allergic reaction includes a severe rash, hives, breathing problems, or dizziness.
- you had surgery less than 12 - 24 hours ago and you were not taking OxyContin just before surgery.

Your doctor should know about all your medical conditions before deciding if OxyContin is right for you and what dose is best. Tell your doctor about all of your medical problems, especially the ones listed below:

- trouble breathing or lung problems
- head injury
- liver or kidney problems
- adrenal gland problems, such as Addison's disease
- convulsions or seizures
- alcoholism
- hallucinations or other severe mental problems
- past or present substance abuse or drug addiction

If any of these conditions apply to you, and you haven't told your doctor, then you should tell your doctor before taking OxyContin.

If you are pregnant or plan to become pregnant, talk with your doctor. OxyContin may not be right for you. **Tell your doctor if you are breast-feeding**. OxyContin will pass through the milk and may harm the baby.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. They may cause serious medical problems when taken with OxyContin, especially if they cause drowsiness.

How Should I Take OxyContin®?

- **Follow your doctor's directions exactly**. Your doctor may change your dose based on your reactions to the medicine. Do not change your dose unless your doctor tells you to change it. Do not take OxyContin more often than prescribed.
- **Swallow the tablets whole**. **Do not break, crush, dissolve, or chew before swallowing. If the tablets are not whole, your body will absorb too much medicine at one time. This can lead to serious problems, including overdose and death.**
- **If you miss a dose**, take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take 2 doses at once unless your doctor tells you to.
- **In case of overdose**, call your local emergency number or Poison Control Center right away.
- **Review your pain regularly with your doctor** to determine if you still need OxyContin.
- **You may see tablets in your stools (bowel movements)**. Do not be concerned. Your body has already absorbed the medicine.

If you continue to have pain or bothersome side effects, call your doctor.

Stopping OxyContin. Consult your doctor for instructions on how to stop this medicine slowly to avoid uncomfortable symptoms. You should not stop taking OxyContin all at once if you have been taking it for more than a few days.

After you stop taking OxyContin, flush the unused tablets down the toilet.

What Should I Avoid While Taking OxyContin®?

- **Do not drive, operate heavy machinery, or participate in any other possibly dangerous activities** until you know how you react to this medicine. OxyContin can make you sleepy.

- **Do not drink alcohol while using OxyContin. It may increase the chance of getting dangerous side effects.**

- **Do not take other medicines without your doctor's approval.** Other medicines include prescription and non-prescription medicines, vitamins, and supplements. Be especially careful about products that make you sleepy.

What are the Possible Side Effects of OxyContin®?

Call your doctor or get medical help right away if
- your breathing slows down
- you feel faint, dizzy, confused, or have any other unusual symptoms

Some of the common side effects of OxyContin® are nausea, vomiting, dizziness, drowsiness, constipation, itching, dry mouth, sweating, weakness, and headache. Some of these side effects may decrease with continued use.

There is a risk of abuse or addiction with narcotic painkillers. If you have abused drugs in the past, you may have a higher chance of developing abuse or addiction again while using OxyContin.

These are not all the possible side effects of OxyContin. For a complete list, ask your doctor or pharmacist.

General Advice About OxyContin

- Do not use OxyContin for conditions for which it was not prescribed.

- Do not give OxyContin to other people, even if they have the same symptoms you have. Sharing is illegal and may cause severe medical problems, including death.

This leaflet summarizes the most important information about OxyContin. If you would like more information, talk with your doctor. Also, you can ask your pharmacist or doctor for information about OxyContin that is written for health professionals.

Rx Only

Purdue Pharma L.P.
Stamford, CT 06901-3431

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